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11 Veröffentlichungsnummer: **0 574 726 A1**

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EUROPÄISCHE PATENTANMELDUNG

21 Anmeldenummer: 93108238.2

22 Anmeldetag: 21.05.93

51 Int. Cl.⁵: **C07D 498/04**, **C07D 271/12**,
A61K 31/41, **A61K 31/435**,
/(C07D498/04,333:00,271:00),
(C07D498/04,271:00,209:00),
(C07D498/04,307:00,271:00),
(C07D498/04,271:00,221:00)

30 Priorität: 10.06.92 DE 4218977

43 Veröffentlichungstag der Anmeldung:
22.12.93 Patentblatt 93/51

84 Benannte Vertragsstaaten:
AT BE CH DE DK ES FR GB GR IE IT LI NL PT SE

71 Anmelder: **CASSELLA Aktiengesellschaft**
Hanauer Landstrasse 526
D-60386 Frankfurt(DE)

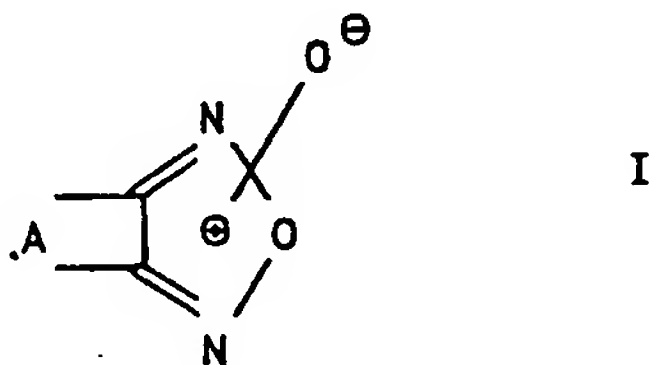
72 Erfinder: **Brendel, Joachim, Dr.**
Landgrabenstrasse 23

D-61118 Bad Vilbel(DE)
Erfinder: **Bohn, Helmut, Dr.**
Am Kranzberggring 11
W-6369 Schöneck 1(DE)
Erfinder: **Schönafinger, Karl, Dr.**
Holunderweg 8
W-8755 Alzenau(DE)

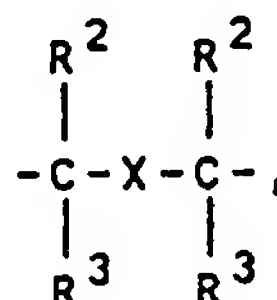
74 Vertreter: **Urbach, Hans-Georg, Dr.**
CASSELLA AKTIENGESELLSCHAFT,
Patentabteilung,
Hanauer Landstrasse 526
D-60386 Frankfurt (DE)

54 Anellierte 1,2,5-Oxadiazol-2-oxide und ihre Verwendung als pharmakologische Wirkstoffe.

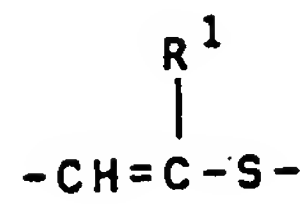
57 Die vorliegende Erfindung betrifft anellierte 1,2,5-Oxadiazol-2-oxide der allgemeinen Formel I



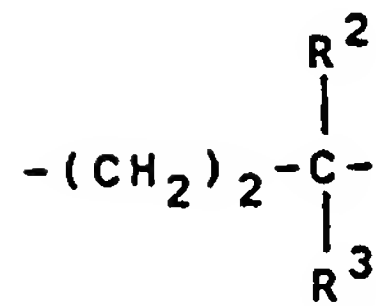
worin
A



-(CH₂)_n-Y-, -CH₂-Z-CO-,



oder



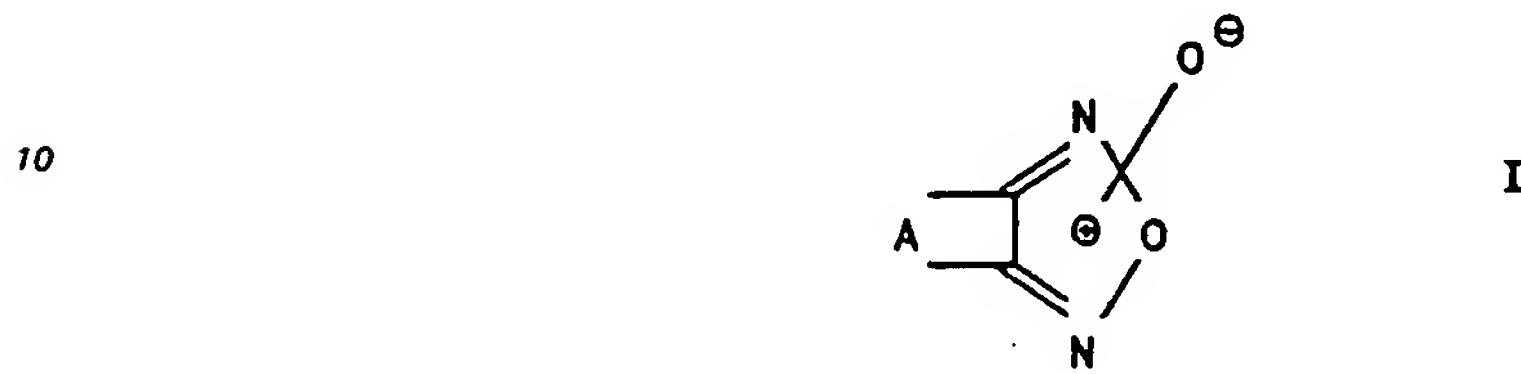
bedeutet;

und X, Y, Z sowie R¹, R², R³ und n wie in Anspruch 1 angegeben definiert sind, Verfahren zu ihrer Herstellung und ihre Verwendung.

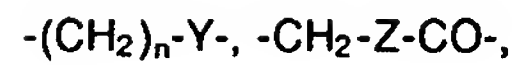
Die vorliegende Erfindung betrifft annellierte 1,2,5-Oxadiazol-2-oxide, ihre Herstellung und ihre Verwendung als pharmakologische Wirkstoffe.

Eine Reihe von annellierten 1,2,5-Oxadiazol-2-oxiden sind bereits bekannt und beispielsweise in der DE-A 29 12 447 beschrieben.

5 Die vorliegende Erfindung betrifft annellierte 1,2,5-Oxadiazol-2-oxide der allgemeinen Formel I



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worin
A



oder



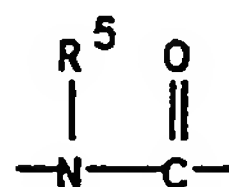
bedeutet;

n für 2 oder 3 steht;

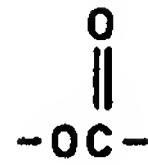
X -O-, -N(R²)-, -N(COR⁴)-, -S-, -S(O)-, -S(O)₂-, -CH₂- oder -CH₂CH₂- bedeutet;

Y -S-, -S(O)-, -S(O)₂-,

50



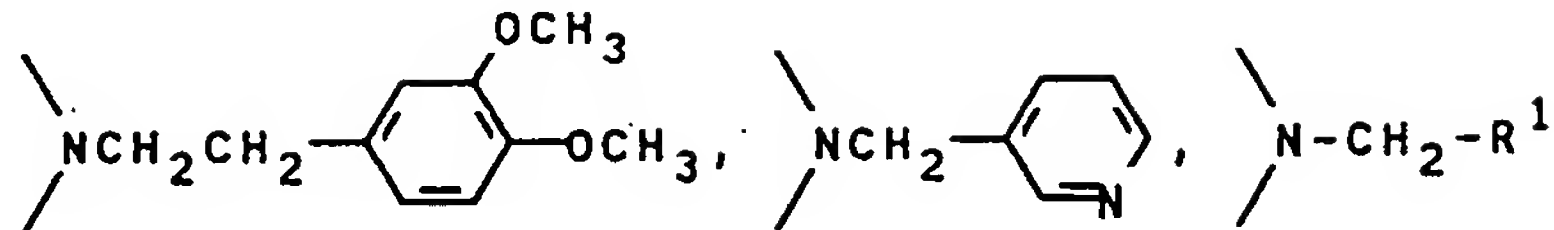
oder



5

bedeutet;
Z $-\text{C}(\text{R}^2\text{R}^3)-$, $-\text{O}-$, $-\text{S}-$, $\text{N}(\text{H})-$, $\text{N}(\text{CH}_3)-$,

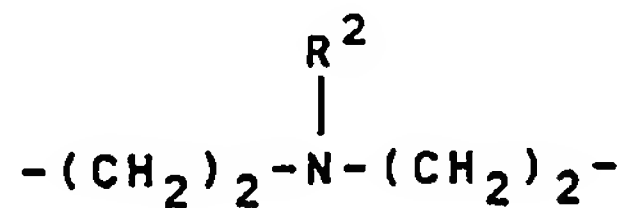
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oder $-\text{CH}_2-$ bedeutet;
R¹ $-\text{COOH}$, $-\text{COOR}^6$ oder $-\text{CONR}^2\text{R}^3$ bedeutet;
R² Wasserstoff oder (C_1-C_6) -Alkyl bedeutet;
R³ (C_1-C_6) -Alkyl bedeutet;
R⁴ Wasserstoff, (C_1-C_6) -Alkyl, oder gegebenenfalls substituiertes Aryl bedeutet;
R⁵ Wasserstoff, (C_1-C_6) -Alkyl, (C_2-C_4) -Alkenyl, gegebenenfalls substituiertes Aryl,
25 $-(\text{CH}_2)_p-\text{R}^7$, $-\text{CH}_2\text{COOR}^2$, $-\text{CH}_2\text{CONR}^2\text{R}^3$, $-\text{CH}_2\text{CON B}$ oder
30 $-\text{CH}_2)_r\text{D}$ bedeutet;
R⁶ (C_2-C_4) -Alkyl bedeutet;
R⁷ gegebenenfalls substituiertes Aryl oder Heteroaryl bedeutet;
B $-(\text{CH}_2)_q-$, $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$ oder

30



35

bedeutet;
D $-\text{OH}$, $-\text{OR}^2$ oder $-\text{NR}^2\text{R}^3$ bedeutet; sowie
p für 1, 2 oder 3;
40 q für 4, 5 oder 6; und
r für 2, 3 oder 4 steht,

sowie deren pharmakologisch annehmbare Säureadditionsverbindungen.

Für R², R³, R⁴, R⁵ oder R⁶ stehende Alkylreste können geradkettig oder verzweigt sein. Beispiele für solche Alkylreste sind Methyl, Ethyl, n-Propyl, i-Propyl, n-Butyl, i-Butyl, Pentyl und Hexyl.

45 Für R⁵ stehendes (C_2-C_4) -Alkenyl kann ebenfalls geradkettig oder verzweigt sein. Beispiele sind Vinyl und Allyl.

Für R⁴, R⁵ oder R⁷ stehendes Aryl ist insbesondere $(\text{C}_6-\text{C}_{14})$ -Aryl, wobei Phenyl bevorzugt ist.

Für R⁷ stehendes Heteroaryl ist bevorzugt 5- bis 7-gliedrig und leitet sich beispielsweise von Pyrrol oder Pyridin ab. Bevorzugt sind α -Pyridyl und β -Pyridyl.

50 Für R⁴, R⁵ oder R⁷ stehendes Aryl und Heteroaryl können auch substituiert sein. Geeignete Substituenten sind beispielsweise (C_1-C_4) -Alkyl, (C_1-C_4) -Alkoxy, Amino, (C_1-C_4) -Alkylamino, Di- (C_1-C_4) -alkylamino, (C_1-C_6) -Alkanoylamino, Halogen, vorzugsweise Fluor, Chlor oder Brom, Hydroxy, Nitro oder Cyano. Aryl oder Heteroaryl können durch die genannten Substituenten auch mehrfach, beispielsweise zwei- oder dreifach substituiert sein.

55 Ein bevorzugter substituiertes Arylrest ist 3,4-Dimethoxyphenyl.

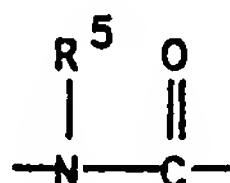
Bevorzugt sind ferner:

n 2
R² Wasserstoff, Methyl

	R ³	Methyl, Ethyl
	R ⁴	Methyl, Phenyl
	R ⁶	Ethyl
	R ⁷	Phenyl, 3,4-Dimethoxyphenyl, 2-Pyridyl, 3-Pyridyl
5	p	1, 2
	q	4, 5
	r	2, 3

Besonders bevorzugt sind:

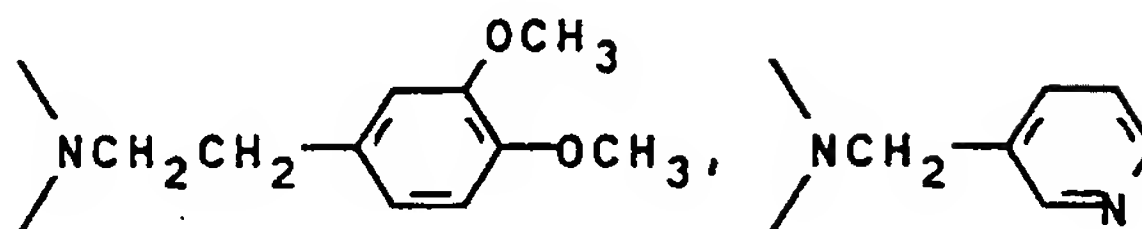
	X	-O-, -N(H)-, -N(CH ₃)-, N(CO-Phenyl)-, -N(COCH ₃)-, -CH ₂ -, -CH ₂ CH ₂ -
10	Y	-S(O) ₂ -,



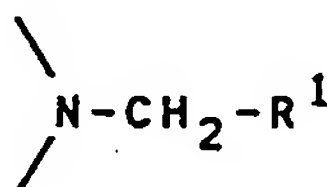
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Z -N(H)-, -N(CH₃)-,

20



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30

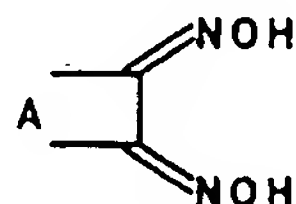
R¹ -COOH, -COOC₂H₅, -COONHCH₃

R⁵ Wasserstoff, -CH₃, -C₂H₅, -Phenyl, -(CH₂)_p-R⁷,

35 -CH₂COOR², -CH₂CONR²R³, -CH₂CON B, -(CH₂)_rD

Die erfindungsgemäßen Verbindungen der allgemeinen Formel I können dadurch hergestellt werden, daß 1,2-Dioxime der allgemeinen Formel II

40



II

45 worin A wie oben angegeben definiert ist, oxidiert werden.

Als Oxidationsmittel für diese an sich bekannte Reaktion können Hypohalogenite wie Natrium- oder Kaliumhypochlorit oder -bromit, Metallsalze wie Kaliumhexacyanoferrat (III) oder Bleitetraacetat, nitrose Gase wie NO₂ oder Iodosoverbindungen wie z.B. Bis-(trifluoracetoxy)-iodbenzol eingesetzt werden.

Aus Dioximen der allgemeinen Formel II mit unsymmetrischem Rest A können in Abhängigkeit von der Konfiguration der eingesetzten Oxime und den angewendeten Reaktionsbedingungen zwei Isomere der allgemeinen Formel I mit unterschiedlicher Lage der N-Oxid-Funktion, d.h. 1-Oxid- oder 3-Oxid-Verbindungen, entstehen.

Verbindungen der allgemeinen Formel I mit A = -(CH₂)_nY- oder -CH₂-Z-CO- lassen sich durch Erhitzen auf 80 bis 140°C in einem inerten Lösungsmittel, wie beispielsweise Toluol oder Petrolether, ineinander umlagern. Aus den so erhaltenen Gleichgewichtsgemischen können die einzelnen Isomere durch übliche Trennverfahren, wie beispielsweise Kristallisation oder Chromatographie als reine Verbindungen isoliert werden.

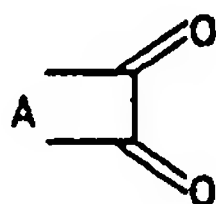
Für die Anwendungen der Verbindungen der allgemeinen Formel I ist die Trennung der Isomeren jedoch nicht zwingend erforderlich, so daß sie auch unterbleiben kann.

Bei Verbindungen der allgemeinen Formel I mit $A = -CH=CR^1-S-$ ist eine solche Trennung nicht möglich, weil sich diese Isomere bereits bei Raumtemperatur rasch ineinander umwandeln.

Die vorliegende Erfindung betrifft demnach auch Isomerengemische von annellierten 1,2,5-Oxadiazol-2-oxiden der allgemeinen Formel I, worin

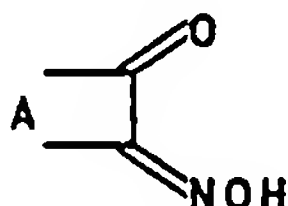
A $-(CH_2)_n-Y-$, $-CH_2-Z-CO-$, $-CH=CR^1-S$ oder $-(CH_2)_2CR^2R^3$ -bedeutet und Y, Z, R^1 , R^2 , R^3 und n wie oben angegeben definiert sind.

Die 1,2-Dioxime der allgemeinen Formel II können entweder aus 1,2-Dionen der allgemeinen Formel III



III

oder aus 1,2-Dionmonooximen der allgemeinen Formel IV

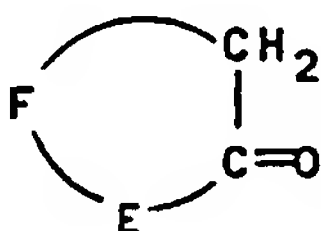


IV

durch Umsetzung mit überschüssigem Hydroxylamin erhalten werden (siehe z.B. Houben-Weyl, Methoden der organischen Chemie, Band X/4, Seite 55 bis 77).

Die Verbindungen der allgemeinen Formeln III und IV sind entweder bekannt oder lassen sich nach bekannten Methoden herstellen.

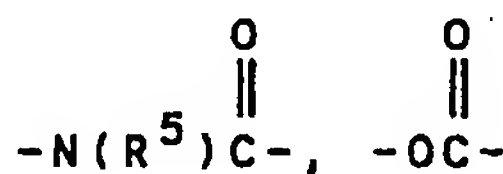
Beispielsweise können Verbindungen der allgemeinen Formel V



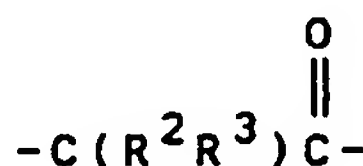
V

worin

E $-C(R^2R^3)-$,



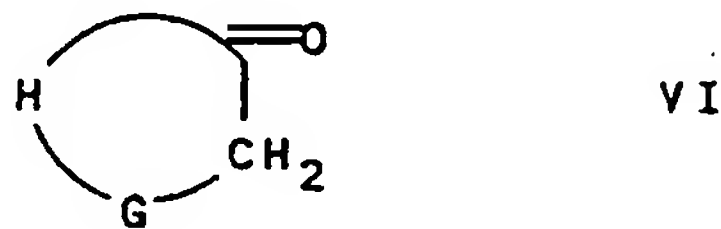
oder



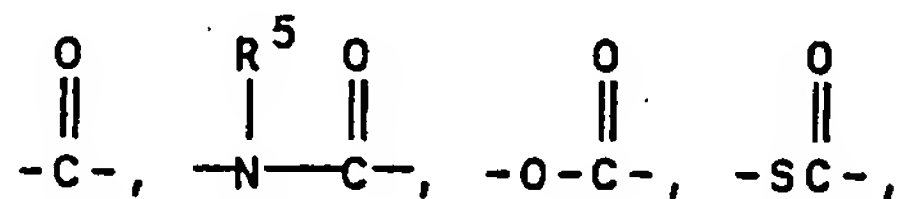
bedeutet, F so gewählt ist, daß E und F zusammen A entsprechend obiger Definitionen ergeben und R^2 , R^3 und R^5 wie oben angegeben definiert sind, durch Nitrosierung der Methylengruppe, beispielsweise mit Natriumnitrit in Salz- oder Essigsäure (siehe z.B. H. v. Dobeneck et al., Liebigs Ann. Chem. 1976, 476) oder mit Amylnitrit in Gegenwart eines Alkalimetallalkoholats (siehe z.B. C. Sandris, G. Ourisson, Bull. Soc. Chim. Fr. 1958, 345, Houben-Weyl, Band X/4, Seite 17 - 44), in Dionmonooxime der allgemeinen Formel IV oder

alternativ durch Oxidation, beispielsweise mit Seldioxid (siehe z.B. C. Sandris, G. Ourisson, Bull. Soc. Chim. Fr. 1958, 345, Houben-Weyl, Band 4/1a, Seite 351 - 353), in Dione der allgemeinen Formel III überführt werden.

Alternativ können aber auch Verbindungen der allgemeinen Formel VI



worin
G

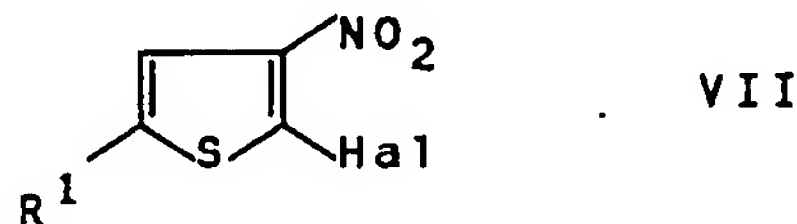


-S-, -S(O) oder

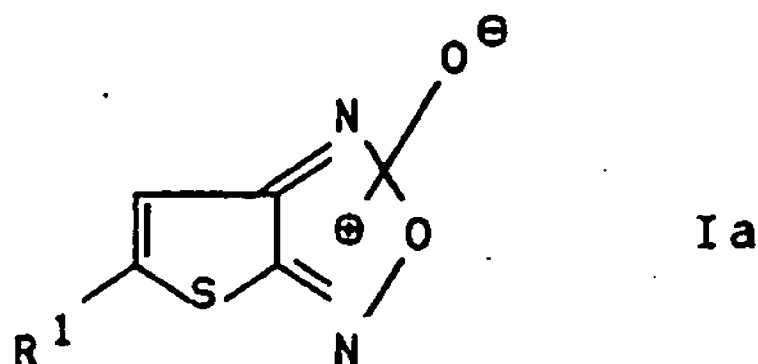
-S(O)₂ bedeutet, H so gewählt wird, daß G und H zusammen A entsprechend obiger Definitionen ergeben und R⁵ wie oben angegeben definiert ist, durch Reaktion mit Natriumnitrit in wäßriger Salzsäure nitrosiert werden. Man erhält dadurch ebenfalls Verbindungen der allgemeinen Formel IV (siehe z.B. J. Ackrell, A. J. Boulton, J. Chem. Soc. Perkin Trans. I 1973, 351).

Die Herstellung von Verbindungen der allgemeinen Formel VI ist bekannt und beispielsweise in EP-A 149 534, J. Antibiotics 33 (1980), 173 und J. Chem. Soc. (C) 1967, 2171 beschrieben.

Für die Synthese von Verbindungen der allgemeinen Formel I mit A = -CH=C(R¹)-S- ist es bevorzugt, eine Verbindung der allgemeinen Formel VII



worin Hal Chlor oder Brom bedeutet und R¹ wie oben angegeben definiert ist, mit Natriumazid in erfindungsgemäße Verbindungen der allgemeinen Formel Ia



zu überführen (siehe z.B. J. Chem. Soc. Perkin Trans II, 1989, 127).

Gemäß den vorstehenden Herstellungsverfahren können neben den in den Beispielen beschriebenen, auch die folgenden erfindungsgemäßen Verbindungen hergestellt werden:

5-Phenyl-6,7-dihydro[1,2,5]oxadiazolo-[3,4-c]pyridin-4-(5H)-on-1-oxid und -3-oxid, sowie die entsprechenden 5-(3-Pyridylmethyl)-, 5-Methyl-, 5-Ethyl-, 5-Propyl-, 5-Isopropyl-, 5-Butyl-, 5-Hexyl-, 5-Allyl-, 5-(3,4-Dimethoxybenzyl)-, 5-(3,4-Dimethoxyphenylethyl)-, 5-(N,N-Diethylaminoethyl)-, 5-(N,N-Dimethylaminocarbonylmethyl)- und 5-Hydroxyethylverbindungen;

6,7-Dihydro[1,2,5]oxadiazolo[3,4-c]pyridin-4(5H)-on-1-oxid und -3-oxid;

5,6,7,8-Tetrahydro[1,2,5]oxadiazolo-[3,4-c]azepin-4-on-1-oxid und -3-oxid;

- 5-Benzyl-5,6,7,8-tetrahydro[1,2,5]oxadiazolo-[3,4-c]azepin-4-on-1-oxid und -3-oxid, sowie die entsprechenden 5-(3-Pyridylmethyl)-Verbindungen;
 5,6-Dihydro-thieno[2,3-c][1,2,5]oxadiazol-1-oxid und -3-oxid sowie die entsprechenden 4-oxo-Derivate;
 6,7-Dihydro[1,2,5]oxadiazolo[3,4-c]pyran-4-on-1-oxid und -3-oxid;
 5 5-Methyl-5,6-dihydro-4,4,6,6-tetramethyl-4H-pyrrolo-[3,4-c][1,2,5]oxadiazol-1-oxid sowie die entsprechende 5-Acetyl-Verbindung;
 4,5,6,7-Tetrahydro-4,4,7,7-tetramethylbenzofurazan-1-oxid;
 4,5,6,7-Tetrahydro-4,7-dimethylbenzofurazan-1-oxid;
 5,6-Dihydro-cyclopent[c][1,2,5]oxadiazol-4(4H)-on-1-oxid und -3-oxid;
 10 5,6-Dihydro-5,5-dimethyl-cyclopent[c][1,2,5]oxadiazol-4(4H)-on-1-oxid und -3-oxid;
 Thieno[2,3-c][1,2,5]oxadiazol-5-carbonsäure-1-oxid und -3-oxid sowie die entsprechenden 5-Carbonsäureethylamid-Verbindungen;
 4-Methyl- und 6-Methyl-5,6-dihydro-4H-cyclopent [c]-[1,2,5]oxadiazol-1-oxid sowie die entsprechenden 4,4-Diethyl- und 6,6-Diethyl-Verbindungen;
 15 4H, 6H-4,6-Dimethylfuro[3,4-c][1,2,5]oxadiazol-1-oxid;
 4H, 6H-Furo[3,4-c][1,2,5]oxadiazol-4-on-1-oxid und -3-oxid sowie die entsprechenden 4H, 6H-Thieno-Verbindungen;
 5,6-Dihydro-5-(3-pyridylmethyl)-4H-pyrrolo[3,4-c][1,2,5]-oxadiazol-4-on-1-oxid und -3-oxid sowie die entsprechenden 5-Hydroxycarbonylmethylverbindungen.

20 Erfindungsgemäße Verbindungen der allgemeinen Formel I, die eine basische Gruppe enthalten, können mit anorganischen oder organischen Säuren Salze bilden. Geeignete Säuren für die Bildung pharmakologisch annehmbarer Säureadditionssalze sind beispielsweise: Chlorwasserstoff, Bromwasserstoff, Naphthalindisulfonsäuren, insbesondere Naphthalindisulfonsäure(1,5), Phosphor-, Salpeter-, Schwefel-, Oxal-, Milch-, Wein-, Essig-, Salicyl-, Benzoe-, Ameisen-, Propion-, Pivalin-, Diethylessig-, Malon-, Bernstein-,
 25 Pimelin-, Fumar-, Malein-, Apfel-, Sulfamin-, Phenylpropion-, Glucon-, Ascorbin-, Isonicotin-, Methansulfon-, p-Toluolsulfon-, Zitronen- oder Adipinsäure. Die Säureadditionssalze können wie üblich durch Vereinigung der Komponenten, zweckmäßigerweise in einem geeigneten Lösungs- oder Verdünnungsmittel, hergestellt werden.

Die Verbindungen der allgemeinen Formel I und ihre pharmakologisch annehmbaren Säureadditionssalze besitzen wertvolle pharmakologische Eigenschaften. Am Modell der Kalium-depolarisierten Pulmonalarterie des Meerschweinchen führen sie in niedrigen Konzentrationen zu einer Relaxation. Diese Wirkung kann mit Oxyhämoglobin inhibiert werden, was auf einen NO-medierten Mechanismus deutet.

Stickstoffmonoxid führt als Aktivator der Guanylatcyclase zu einer Erhöhung von cyclischem Guanosinmonophosphat, welches im glatten Muskel eine Relaxation und in den Blutplättchen antiadhäsive und
 35 antiaggregatorische Wirkungen verursacht. Stickstoffmonoxid ist außerdem auch entscheidend beteiligt bei Lernvorgängen, bei der Regulation der Nierenfunktion, bei der Immunabwehr, beim septischen Schock und bei erektilen Dysfunktionen. Die Verbindungen der allgemeinen Formel I ihre pharmakologisch annehmbaren Säureadditionssalze sowie ihre Isomerengemische können somit bei den genannten Indikationen eingesetzt werden. Vor allem aber haben sich NO-Donoren zur Behandlung und Prophylaxe von angina
 40 pectoris bewährt.

Die Verbindungen der allgemeinen Formel I und ihre pharmakologisch annehmbaren Säureadditionssalze sowie Isomerengemische können daher am Menschen als Heilmittel für sich allein, in Mischungen untereinander oder in Form von pharmazeutischen Zubereitungen verabreicht werden, die eine enterale oder parenterale Anwendung gestatten und die als aktiven Bestandteil eine wirksame Dosis mindestens
 45 einer Verbindung der allgemeinen Formel I oder eines Säureadditionssalzes davon oder eines Isomerengemisches, neben üblichen pharmazeutisch einwandfreien Träger- und Zusatzstoffen enthalten.

Die Heilmittel können oral, z.B. in Form von pillen, Tabletten, Lacktabletten, Dragees, Hart- und Weichgelatine kapseln, Lösungen, Sirupen, Emulsionen oder Suspensionen oder Aerosolmischungen verabreicht werden. Die Verabreichung kann aber auch rektal, z.B. in Form von Suppositorien, oder parenteral,
 50 z.B. in Form von Injektionslösungen, oder perkutan, z.B. in Form von Salben oder Tinkturen, erfolgen.

Zur Herstellung der pharmazeutischen Präparate können pharmazeutisch inerte anorganische oder organische Trägerstoffe verwendet werden. Für die Herstellung von Pillen, Tabletten, Dragees und Hartgelatine kapseln kann man z.B. Lactose, Maisstärke oder Derivate davon, Talk, Stearinsäure oder deren Salze etc. verwenden. Trägerstoffe für Weichgelatine kapseln und Suppositorien sind z.B. Fette, Wachse, halbfeste und flüssige Polyole, natürliche oder gehärtete Öle etc. Als Trägerstoffe für die Herstellung von Lösungen und Sirupen eignen sich z.B. Wasser, Saccharose, Invertzucker, Glukose, Polyole etc. Als Trägerstoffe für
 55 die Herstellung von Injektionslösungen eignen sich z.B. Wasser, Alkohole, Glyzerin, Polyole oder pflanzliche Öle.

Die pharmazeutischen Präparate können neben den Wirk- und Trägerstoffen noch Zusatzstoffe, wie z.B. Füllstoffe, Streck-, Spreng-, Binde-, Gleit-, Netz-, Stabilisierungs-, Emulgier-, Konservierungs-, Süß-, Färbe-, Geschmacks- oder Aromatisierungs-Mittel, Puffersubstanzen, ferner Lösungsmittel oder Lösungsvermittler oder Mittel zur Erzielung eines Depoteffekts, sowie Salze zur Veränderung des osmotischen Drucks, Überzugsmittel oder Antioxidantien enthalten. Sie können auch zwei oder mehrere Verbindungen der allgemeinen Formel I oder ihrer pharmakologisch annehmbaren Säureadditionssalze und noch andere therapeutisch wirksame Stoffe enthalten.

Derartige andere therapeutisch wirksame Substanzen sind beispielsweise: β -Rezeptorenblocker, wie z.B. Propranolol, Pindolol, Metoprolol; Vasodilatoren, wie z.B. Carbocromen; Beruhigungsmittel, wie z.B. Barbitursäurederivate, 1,4-Benzodiazepine und Meprobamat; Diuretica, wie z.B. Chlorothiazid; das Herz tonisierende Mittel, wie z.B. Digitalispräparate; blutdrucksenkende Mittel, wie z.B. Hydralazin, Dihydralazin, Ramipril, Prazosin, Clonidin, Rauwolfia-Alkaloide; Mittel, die den Fettsäurespiegel im Blut senken, wie z.B. Bezafibrat, Fenofibrat; Mittel für die Thromboseprophylaxe, wie z.B. Phenprocoumon.

Die Verbindungen der allgemeinen Formel I, ihre pharmakologisch annehmbaren Säureadditionssalze, ihre Isomerengemische und pharmazeutische Präparate, welche die Verbindungen der allgemeinen Formel I oder ihre pharmakologisch annehmbaren Säureadditionssalze oder ein Isomerengemisch als Wirkstoffe enthalten, können am Menschen bei der Bekämpfung bzw. Vorbeugung von Erkrankungen des kardiovaskulären Systems verwendet werden, beispielsweise als antihypertensive Heilmittel bei den verschiedenen Formen des Bluthochdrucks, bei der Bekämpfung bzw. Vorbeugung von Angina pectoris usw. Darüber hinaus können sie auch zur Behandlung erektiler Dysfunktionen eingesetzt werden. Die Dosierung kann innerhalb weiter Grenzen variieren und ist in jedem einzelnen Fall den individuellen Gegebenheiten anzupassen. Im allgemeinen ist bei oraler Verabreichung pro menschlichem Individuum eine Tagesdosis von etwa 0,5 bis 100 mg, vorzugsweise 1 bis 20 mg, angemessen. Auch bei anderen Applikationsformen liegt die Tagesdosis, wegen der guten Resorption der Wirkstoffe, in ähnlichen Mengenbereichen, d.h. im allgemeinen ebenfalls bei 0,5 bis 100 mg/Mensch. Die Tagesdosis wird normalerweise in mehrere, z.B. 2 bis 4 Teilverabreichungen aufgeteilt.

Beispiel 1:

5,6-Dihydro-4,4-dioxothieno[2,3-c][1,2,5]oxadiazol-1-oxid und -3-oxid

a) Zu einer Suspension von 15,5 g (116 mmol) 3-Oxotetrahydrothiophendioxid (M.A. Smith et al., J. Chem. Soc. (c) 1967, 2171) in 70 ml Wasser und 10 ml konz. Salzsäure wird bei 0°C eine Lösung von 8,4 g (120 mmol) Natriumnitrit in 25 ml Wasser zugetropft. Nach 1 Stunde bei 0°C wird das Produkt abgesaugt, mit Wasser gewaschen und im Vakuum getrocknet. Man erhält 11,5 g (61 %) 2-Hydroxyimino-3-oxotetrahydrothiophendioxid, Fp. 148°C.

b) Zu einer Lösung von 11,4 g (70 mmol) 2-Hydroxyimino-3-oxotetrahydrothiophendioxid in 100 ml Methanol werden 5,4 g (77 mmol) Hydroxylaminhydrochlorid gelöst in 15 ml Wasser zugegeben. Nach 2 Stunden bei Raumtemperatur wird der Ansatz vollständig eingeeengt und der Rückstand aus Ethanol umkristallisiert. Man erhält 6,2 g (50 %) 2,3-Dihydroxyiminotetrahydrothiophendioxid, Fp. 181°C.

c) Zu einer Suspension von 1,5 g (8,4 mmol) 2,3-Dihydroxyiminotetrahydrothiophendioxid in 250 ml CH_2Cl_2 wird eine Lösung von 4,4 g (10 mmol) Bis(trifluoracetoxy)-iodbenzol in 280 ml CH_2Cl_2 zugetropft und 1 Stunde bei Raumtemperatur gerührt. Aus dem vollständig eingeeengten Ansatz kristallisiert das Produkt über Nacht teilweise aus. Nach Verrühren mit Isopropanol erhält man 1,0 g (68 %) 5,6-Dihydro-4,4-dioxo-thieno[2,3-c][1,2,5]oxadiazol-1-oxid und -3-oxid im Verhältnis 1 : 1 (NMR), Fp. 76°C.

Beispiel 2:

4H, 6H-4,4,6,6-Tetramethylfuro[3,4-c][1,2,5]oxadiazol-1-oxid

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a) 10,0 g (54 mmol) käufliches 2,2,5,5-Tetramethyl-3,4-(2H,5H)-furandionhydrazonoxim werden in 800 ml Wasser mit 75 g (1,1 mmol) Hydroxylaminhydrochlorid 2 Stunden unter Rückfluß erhitzt. Das ausgefallene Produkt wird abgesaugt und mit Wasser gewaschen. Man erhält 8 g (86 %) 2,2,5,5-Tetramethyl-3,4-(2H,5H)-furandiondioxim als Gemisch von 2 Isomeren, Fp. 252°C.

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b) Zu einer Lösung von 3,0 g (16 mmol) 2,2,5,5-Tetramethyl-3,4-(2H,5H)-furandiondioxim in 15 ml 10 %ige Natronlauge werden 90 ml 14 %ige Natriumhypochloritlösung bei 0°C rasch zugegeben. Der ausgefallene Niederschlag wird sofort abgesaugt, mit Wasser gewaschen und aus Isopropanol umkristallisiert. Man erhält 2,0 g (67 %) 4H,6H-4,4,6,6-Tetramethylfuro[3,4-c][1,2,5]oxadiazol-1-oxid, Fp. 121°C.

Beispiel 3:

4-Ethyl- und 6-Ethyl-5,6-dihydro-4H-cyclopent[c][1,2,5]-oxadiazol-1-oxid

- 5 a) Zu einer Lösung von 14 g (200 mmol) Hydroxylaminhydrochlorid und 16,5 g (200 mmol) Natriumacetat in 150 ml Wasser wird bei 60°C eine Lösung von 5,0 g (40 mmol) 3-Ethyl-2-hydroxy-2-cyclopenten-1-on in 5 g 1,2-Propandiol zugetropft. Nach 2 Stunden bei 70°C wird der ausgefallene Niederschlag abgesaugt und mit Wasser gewaschen. Man erhält 5,0 g (81 %) 3-Ethylcyclopentan-1,2-diondioxim.
- 10 b) Zu einer Lösung von 5,0 g (32 mmol) 3-Ethylcyclopentan-1,2-diondioxim in 200 ml 10 %iger Natronlauge werden 200 ml 14 %ige Natriumhypochloritlösung bei 0°C zugetropft. Nach Extrahieren mit Essigester und Destillieren im Vakuum bei 104°C/0,1 Torr erhält man 3,0 g (60 %) 4-Ethyl- und 6-Ethyl-5,6-dihydro-4H-cyclopent[c][1,2,5]-oxadiazol-1-oxid im Verhältnis 1 : 1 (NMR).

Beispiel 4:

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5-Benzoyl-5,6-dihydro-4,4,6,6-tetramethyl-4H-pyrrolo-[3,4-c][1,2,5]oxadiazol-1-oxid.

- a) Eine Lösung von 0,7 g (2,7 mmol) 1-Benzoyl-2,2,5,5-tetramethylpyrrolidin-3,4-dion (C. Sandris, G. Ourisson, Bull. Soc. Chim. Fr. 1958, 345) und 1,1 g (16 mmol) Hydroxylaminhydrochlorid in 60 ml
- 20 Ethanol/Wasser (1 : 1) wird 10 Stunden auf 60°C erhitzt. Der ausgefallene Niederschlag wird abgesaugt, mit Wasser gewaschen und im Vakuum getrocknet. Man erhält 0,65 g (83 %) 1-Benzoyl-2,2,5,5-tetramethyl-3,4-pyrrolidindiondioxim, Fp. 235 - 240°C.
- b) 0,55 g (1,9 mmol) 1-Benzoyl-2,2,5,5-tetramethyl-3,4-pyrrolidindiondioxim werden analog Beispiel 2b umgesetzt und man erhält 0,36 g (66 %) 5-Benzoyl-5,6-dihydro-4,4,6,6-tetramethyl-4H-pyrrolo[3,4-c]-
- 25 [1,2,5]oxadiazol-1-oxid, Fp. 147 - 149°C.

Beispiel 5:

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5,6-Dihydro-4,4,6,6-tetramethyl-4H-pyrrolo[3,4-c][1,2,5]-oxadiazol-1-oxid.

Aus 3,1 g (18 mmol) 2,2,5,5-Tetramethylpyrrolidin-3,4-dion-3-oxim werden analog Beispiel 4 1,3 g (45 %) 5,6-Dihydro-4,4,6,6-tetramethyl-4H-pyrrolo[3,4-c][1,2,5]oxadiazol-1-oxid erhalten, ¹³C-NMR (DMSO): δ = 25,0 (q), 27,5 (q), 66,7 (s), 67,7 (s), 115,6 (s), 164,4 (s), Fp. (Hydrochlorid): 184 - 186°C.

35 Beispiel 6:

5,6-Dihydro-5-methyl-4H-pyrrolo[3,4-c][1,2,5]oxadiazol-4-on-1-oxid und -3-oxid.

- 40 a) Zu einer Lösung von 17,0 g (0,15 mol) 1-Methyl-2,3-pyrrolidindion (H. Rapoport et al., J. Org. Chem. 40 (1975) 1264) in 40 ml Eisessig und 30 ml Chloroform werden bei 0°C 10,5 g (0,15 mol) Natriumnitrit in 50 ml Wasser zugetropft. Man rührt noch 2 Stunden, filtriert das ausgefallene Produkt ab und erhält 12,0 g (58 %) 1-Methyl-2,3,4-pyrrolidintrion-4-oxim.
- b) 9,0 g (63 mmol) 1-Methyl-2,3,4-pyrrolidintrion-4-oxim werden mit 15 g Hydroxylaminhydrochlorid und 15 g Natriumacetat 2 Stunden auf 95°C erhitzt, und man erhält 8,5 g (86 %) 1-Methyl-2,3,4-pyrrolidintrion-3,4-dioxim.
- 45 c) Zu einer Suspension von 1,0 g (6,4 mmol) 1-Methyl-2,3,4-pyrrolidintrion-3,4-dioxim in 50 ml Essigester wird eine Lösung von 13,0 g (38 mmol) Kaliumhexacyanoferrat (III) in 40 ml Wasser und 3 ml gesättigter Sodalösung zugetropft, und es wird 2 Stunden bei Raumtemperatur gerührt. Die organische Phase wird abgetrennt, eingeengt und der Rückstand durch Flash-Chromatographie (Essigester/Cyclohexan 60 : 40)
- 50 gereinigt. Man erhält 0,34 g (34 %) 5,6-Dihydro-5-methyl-4H-pyrrolo[3,4-c][1,2,5]oxadiazol-4-on-1-oxid und -3-oxid im Verhältnis 1 : 2 (NMR), Fp. 49 - 52°C.

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Beispiel 7:

Analog Beispiel 6 wurden 5,6-Dihydro-5-(3,4-dimethoxyphenylethyl)-4H-pyrrolo[3,4-c][1,2,5]oxadiazol-4-on-1-oxid und -3-oxid erhalten (Isomere im Verhältnis 1 : 4), Fp. 165°C.

Beispiel 8:

5-Benzyl-6,7-dihydro[1,2,5]oxadiazolo[3,4-c]pyridin-4(5H)-on-1-oxid.

- 10 a) Zu einer Lösung von 7,0 g (34,5 mmol) 1-Benzylpiperidin-2,4-dion (S. Takano et al., Tetrahedron Lett. 1979, 369) in 30 ml Essigester und 30 ml Wasser werden bei 0°C 7 ml konzentrierte Salzsäure zugesetzt und dann 2,5 g (36 mmol) Natriumnitrit in 10 ml Wasser zugetropft. Nach 1 Stunde bei 0°C wird der ausgefallene Niederschlag abgesaugt, und man erhält 6,6 g (85 %) 1-Benzyl-piperidin-2,3,4-trion-3-oxim, Fp. 121 - 122°C.
- 15 b) Aus 4,6 g 1-Benzyl-piperidin-2,3,4-trion-3-oxim werden analog Beispiel 1b 3,4 g (68 %) 1-Benzyl-piperidin-2,3,4-trion-3,4-dioxim, Fp. 170 - 172°C, erhalten.
- c) Zu einer Lösung von 3,0 g (12 mmol) 1-Benzylpiperidin-2,3,4-trion-3,4-dioxim in 80 ml 10 %iger Natronlauge werden 80 ml 14 %ige Natriumhypochloritlösung bei 0°C rasch zugetropft. Der ausgefallene Niederschlag wird sofort abgesaugt, mit Wasser gewaschen und im Vakuum getrocknet. Man erhält 2,6 g (87 %) 5-Benzyl-6,7-dihydro [1,2,5]oxadiazolo[3,4-c]pyridin-4(5H)-on-1-oxid, Fp. 118 - 120°C, ¹H-NMR (DMSO) : δ = 2,95 (t), 3,65 (t), 4,70 (t), 7,35 (s), ¹³C-NMR (DMSO) : δ = 18,0 (t), 44,8 (t), 49,2 (t), 111,9 (s), 127,4 (d), 127,7 (d), 128,5 (d), 136,2 (s), 149,6 (s), 155,7 (s).
- 20

Beispiel 9:

5-Benzyl-6,7-dihydro[1,2,5]oxadiazolo[3,4-c]-pyridin-4(5H)-on-3-oxid.

- 1,6 g 5-Benzyl-6,7-dihydro[1,2,5]oxadiazolo[3,4-c]-pyridin-4(5H)-on-1-oxid werden in 200 ml Toluol 4 Stunden unter Rückfluß erhitzt. Das Toluol wird abgezogen und der Rückstand aus Isopropanol umkristallisiert. Man erhält 1,4 g 5-Benzyl-6,7-dihydro[1,2,5]oxadiazolo[3,4-c]-pyridin-4(5H)-on-3-oxid und -1-oxid im Verhältnis 4 : 1, Fp. 112 - 114°C, ¹H-NMR (DMSO) : δ = 3,10 (t), 3,65 (t), 4,65 (s), 7,35 (s).
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Beispiel 10:

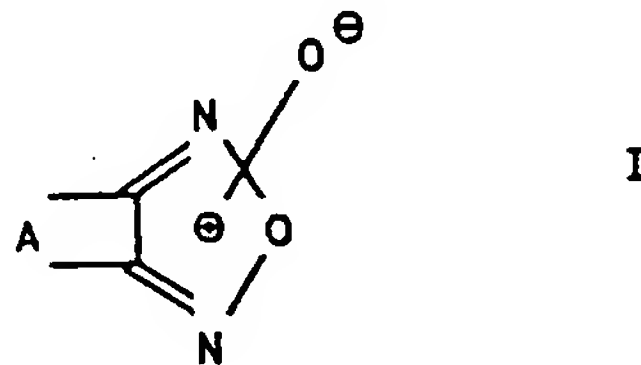
- 35 Thieno[2,3-c][1,2,5]oxadiazol-5-carbonsäureethylester-1-oxid und -3-oxid.

Eine Suspension von 25,0 g (90 mmol) 2-Brom-3-nitro-5-thiophencarbonsäureethylester (Tetrahedron 21 (1965) 1061) und 29,0 g (450 mmol) Natriumazid in 300 ml Methanol wird 4 Stunden bei Raumtemperatur gerührt. Man gießt auf 4 l Eiswasser, filtriert ab und erhitzt den Rückstand in 700 ml Toluol 3 Stunden auf 70°C. Anschließend Reinigung durch Flash-Chromatographie liefert 6,5 g (34 %) Thieno[2,3-c][1,2,5]-oxadiazol-5-carbonsäureethylester-1-oxid und -3-oxid, Fp. 72 - 74°C.

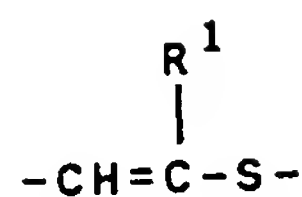
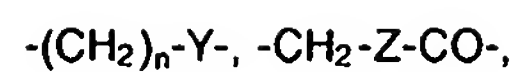
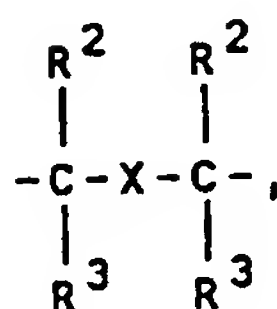
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Patentansprüche

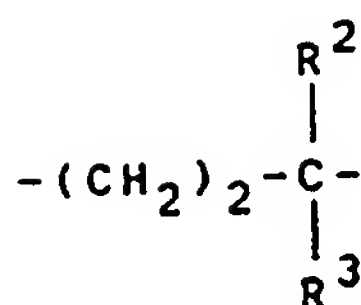
- 45 1. Anellierte 1,2,5-Oxadiazol-2-oxide der allgemeinen Formel I



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worin
A



oder

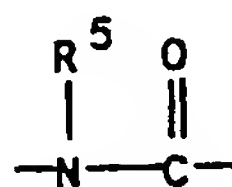


bedeutet;

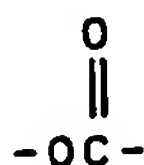
n für 2 oder 3 steht;

X -O-, -N(R²)-, -N(COR⁴)-, -S-, -S(O)-, -S(O)₂-, -CH₂- oder -CH₂CH₂- bedeutet;

Y -S-, -S(O)-, -S(O)₂-,

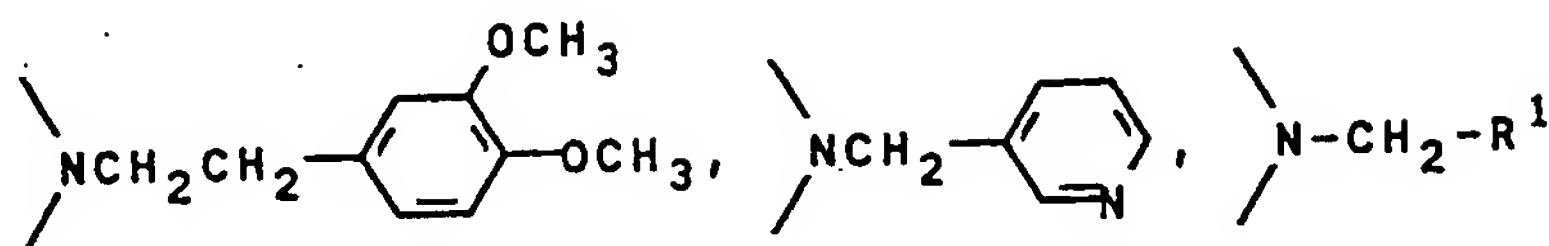


oder



bedeutet;

Z -C(R²R³)-, -O-, -S-, -N(H)-, -N(CH₃)-,

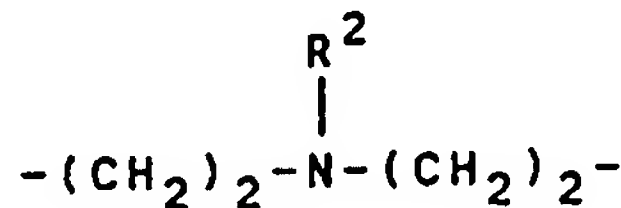


oder -CH₂- bedeutet;

R¹ -COOH, -COOR⁶ oder -CONR²R³ bedeutet;

R² Wasserstoff oder (C₁-C₆)-Alkyl bedeutet;

- R³ (C₁-C₆)-Alkyl bedeutet;
 R⁴ Wasserstoff, (C₁-C₆)-Alkyl, oder gegebenenfalls substituiertes Aryl bedeutet;
 R⁵ Wasserstoff, (C₁-C₆)-Alkyl, (C₂-C₄)-Alkenyl, gegebenenfalls substituiertes Aryl,
 -(CH₂)_p-R⁷, -CH₂COOR², -CH₂CONR²R³, -CH₂CON B oder
 -(CH₂)_rD bedeutet;
 R⁶ (C₂-C₄)-Alkyl bedeutet;
 R⁷ gegebenenfalls substituiertes Aryl oder Heteroaryl bedeutet;
 B -(CH₂)_q-, -(CH₂)₂-O-(CH₂)₂- oder



- bedeutet;
 D -OH, -OR² oder -NR²R³ bedeutet; sowie
 p für 1, 2 oder 3;
 q für 4, 5 oder 6; und
 r für 2, 3 oder 4 steht,
 sowie deren pharmakologisch annehmbare Säureadditionsverbindungen.

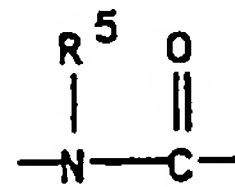
2. Anellierte 1,2,5-Oxadiazol-2-oxide der allgemeinen Formel I nach Anspruch 1, dadurch gekennzeichnet, daß

- n 2
 R² Wasserstoff, Methyl
 R³ Methyl, Ethyl
 R⁴ Methyl, Phenyl
 R⁶ Ethyl
 R⁷ Phenyl, 3,4-Dimethoxyphenyl, 2-Pyridyl, 3-Pyridyl
 p 1, 2
 q 4, 5
 r 2, 3

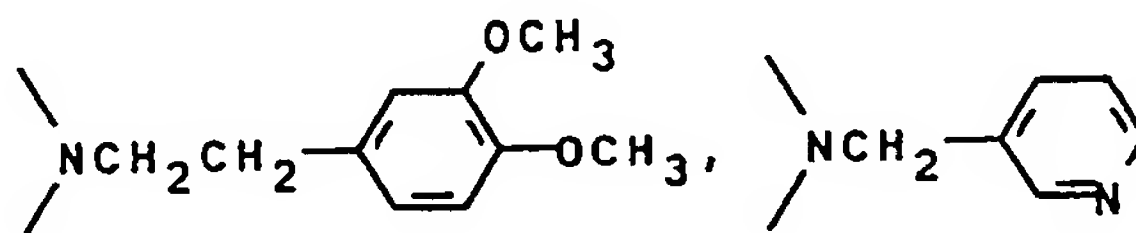
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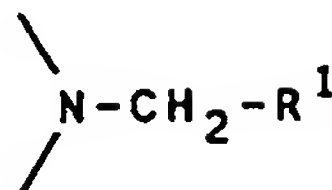
3. Anellierte 1,2,5-Oxadiazol-2-oxide der allgemeinen Formel I nach Anspruch 1 und/oder 2, dadurch gekennzeichnet, daß

- X -O-, -N(H)-, -N(CH₃)-, N(CO-Phenyl)-, -N(COCH₃)-, -CH₂-, -CH₂CH₂-
 Y -S(O)₂-,



- Z -N(H)-, -N(CH₃)-,





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R^1 -COOH, -COOC₂H₅, -COONHCH₃
 R^5 Wasserstoff, -CH₃, -C₂H₅, -Phenyl, -(CH₂)_p-R⁷,
 -CH₂COOR², -CH₂CONR²R³, -CH₂CON B, -(CH₂)_rD

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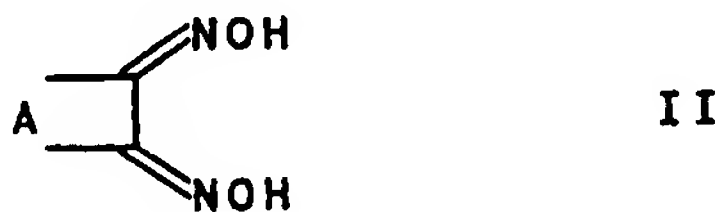
bedeuten.

4. Isomerengemische von annellierten 1,2,5-Oxadiazol-2-oxiden der allgemeinen Formel I gemäß einem oder mehreren der Ansprüche 1 bis 3, worin A -(CH₂)_n-Y-, -CH₂-Z-CO-, -CH=CR¹-S- oder -(CH₂)₂CR²R³ bedeutet und Y, Z, R¹, R², R³ und n wie in Anspruch 1 angegeben definiert sind.

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5. Verfahren zur Herstellung von annellierten 1,2,5-oxadiazol-2-oxiden der allgemeinen Formel I gemäß Anspruch 1, dadurch gekennzeichnet, daß 1,2-Dioxime der allgemeinen Formel II

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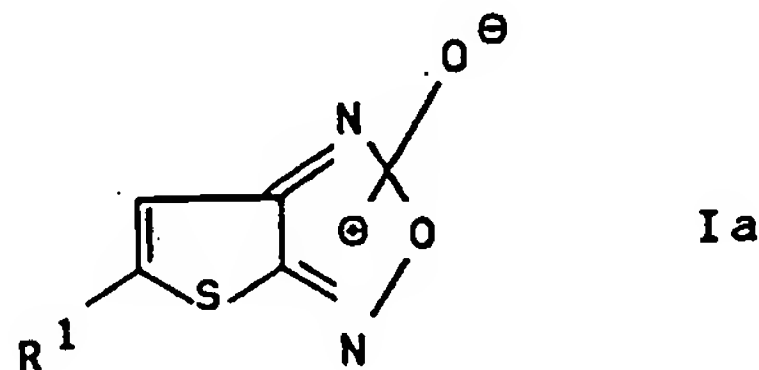


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worin A wie in Anspruch 1 angegeben definiert ist, oxidiert werden.

6. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel Ia

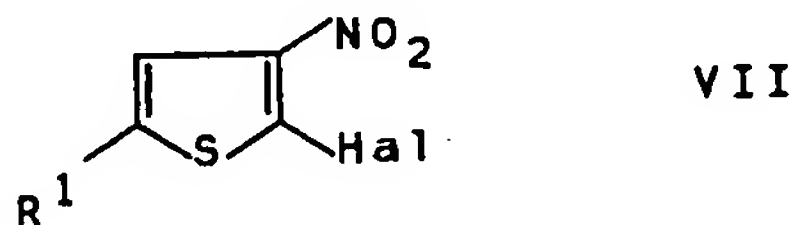
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worin R¹ wie in Anspruch 1 angegeben definiert ist, dadurch gekennzeichnet, daß eine Verbindung der allgemeinen Formel VII

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worin Hal Chlor oder Brom bedeutet, mit Natriumazid umgesetzt wird.

7. Verwendung von annellierten 1,2,5-Oxadiazol-2-oxiden der allgemeinen Formel I gemäß einem oder mehreren der Ansprüche 1 bis 3 zur Bekämpfung und Vorbeugung von Erkrankungen des kardiovaskulären Systems.

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8. Verwendung von annellierten 1,2,5-Oxadiazol-2-oxiden der allgemeinen Formel I gemäß einem oder mehreren der Ansprüche 1 bis 3 zur Bekämpfung und Vorbeugung von Angina pectoris.

9. Verwendung von annellierten 1,2,5-Oxadiazol-2-oxiden der allgemeinen Formel I gemäß einem oder mehreren der Ansprüche 1 bis 3 zur Behandlung erektiler Dysfunktionen.

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10. Pharmazeutisches Präparat, dadurch gekennzeichnet, daß es ein annelliertes 1,2,5-Oxadiazol-2-oxid der allgemeinen Formel I gemäß einem oder mehreren der Ansprüche 1 bis 3, ein pharmakologisch annehmbares Säureadditionssalz davon oder ein Isomerengemisch gemäß Anspruch 4 als Wirkstoff zusammen mit pharmazeutisch annehmbaren Träger- und Zusatzstoffen und gegebenenfalls noch ein
5 oder mehrere andere pharmakologische Wirkstoffe enthält.

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Europäisches
Patentamt

EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung

EP 93 10 8238

EINSCHLÄGIGE DOKUMENTE			
Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int. Cl.5)
D,X	GB-A-2 017 690 (IMPERIAL CHEMICAL INDUSTRIES) * Anspruch 1 *	1	C07D498/04 C07D271/12 A61K31/41 A61K31/435
D,X	JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 2. Nr. 2, 1989, LETCHWORTH GB Seiten 127 - 130 R. NOTO ET AL 'Effect of the nature of the starting aromatic ring on the cyclization of o-nitroaryl azides : Kinetic and thermodynamic studies of the conversion of two azido(methoxycarbonyl)nitrothiophenes into methoxycarbonylthienofurazan oxides' * Verbindungen 10,11 *	1	/(C07D498/04, 333:00,271:00) (C07D498/04, 271:00,209:00) (C07D498/04, 307:00,271:00) (C07D498/04, 271:00,221:00)
A	CHEMICAL ABSTRACTS, vol. 113, no. 3, 1990, Columbus, Ohio, US; abstract no. 23596q, V. A. REZNIKOV ET AL 'Interaction of 2-substituted 5,5-dimethyl-4-oxo-1-pyrroline 1-oxides with nucleophilic reagents and synthesis of the pyrrolidone-derived nitroxides' Seite 631 ; * Zusammenfassung * & IZV. AKAD. NAUK. SSSR, SER. KHIM. Nr. 2, 1990, Seiten 390 - 395	1	RECHERCHIERTE SACHGEBIETE (Int. Cl.5) C07D A61K
A	EP-A-0 038 438 (CASSELLA) * Ansprüche 1,8,9 *	1,7,8,10	
A	EP-A-0 431 944 (MERCK & CO) * Ansprüche 1,6,8 *	1,7,10	
Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt			
Recherchenamt DEN HAAG		Abschlußdatum der Recherche 15 SEPTEMBER 1993	Prüfer VOYIAZOGLU D.
KATEGORIE DER GENANNTEN DOKUMENTE X : von besonderer Bedeutung allein betrachtet Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie A : technologischer Hintergrund O : mündliche Offenbarung P : Zwischenliteratur T : der Erfindung zugrunde liegende Theorien oder Grundsätze E : älteres Patentdokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist D : in der Anmeldung angeführtes Dokument L : aus andern Gründen angeführtes Dokument * : Mitglied der gleichen Patentfamilie, übereinstimmendes Dokument			

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) Veröffentlichungsnummer: **0 683 159 A1**

(12)

EUROPÄISCHE PATENTANMELDUNG

(21) Anmeldenummer: 95106885.7

(51) Int. Cl.⁶: **C07D 271/08, A61K 31/41,
C07D 413/12, C07D 498/04**

(22) Anmeldetag: 06.05.95

(30) Priorität: 20.05.94 DE 4417705

(43) Veröffentlichungstag der Anmeldung:
22.11.95 Patentblatt 95/47

(84) Benannte Vertragsstaaten:
AT BE CH DE ES FR GB IT LI NL SE

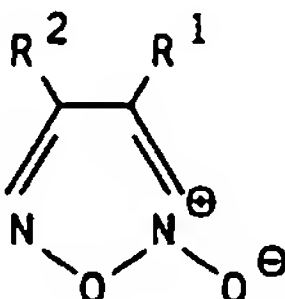
(71) Anmelder: CASSELLA Aktiengesellschaft
Hanauer Landstrasse 526
D-60386 Frankfurt (DE)

(72) Erfinder: Bohn, Helmut, Dr.
Kranzberggring 11
D-61137 Schöneck (DE)
Erfinder: Brendel, Joachim, Dr.
Landgrabenstrasse 23
D-61118 Bad Vilbel (DE)
Erfinder: Schönaflinger, Karl, Dr.
Holunderweg 8
D-63755 Alzenau (DE)
Erfinder: Strobel, Hartmut, Dr.
Wasserloser Strasse 3
D-63755 Alzenau (DE)

(74) Vertreter: Muley, Ralf, Dr.
Cassella AG,
Patentabteilung,
Hanauer Landstrasse 526
D-60386 Frankfurt (DE)

(54) Substituierte Furoxane.

(57) Die vorliegende Erfindung betrifft Furoxane der allgemeinen Formel I



(I)

worin einer der Reste R¹ und R² für -S(O)_n-R³ und der andere für (C₁-C₁₀)-Alkyl, (C₃-C₇)-Cycloalkyl, -CONR⁴R⁵, -CN oder -XR⁶ steht, Verfahren zu ihrer Herstellung und ihre Verwendung.

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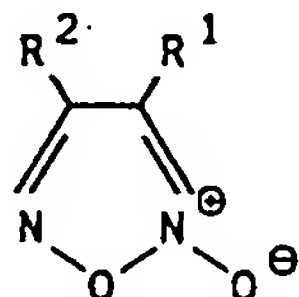
Die vorliegende Erfindung betrifft thio-, sulfinyl- oder sulfonyl-substituierte Furoxane, Verfahren zu ihrer Herstellung und ihre Verwendung.

Es sind bereits verschiedene thio-, sulfinyl- oder sulfonyl-substituierte Furoxane bekannt und beispielsweise beschrieben in J. Chem. Soc. 1964, 904; Synth. Comm. 1, 121 (1971); J. Heterocyclic Chem. 10, 587 (1973); Synth. Comm. 4, 311 (1974); Eur. J. Med. Chem. 1977, 157; J. Heterocyclic Chem. 14, 1415 (1977); Eur. J. Med. Chem. 1980, 485; J. Heterocyclic Chem. 19, 427 (1982); Tetrahedron 41, 727 (1985); Heterocycles 24, 889 (1986); Biochem. Pharm. 43, 1281 (1992); J. Med. Chem. 35, 3296 (1992); J. Chem. Soc. Perkin Trans. 2 1992, 1643; Il Farmaco 48, 321 (1993); EP-A 571 795 und WO 94/01422.

Die vorliegende Erfindung betrifft Furoxane der allgemeinen Formel I

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(I)

20 worin einer der Reste R¹ und R² für -S(O)_n-R³ und der andere für (C₁-C₁₀)-Alkyl, (C₃-C₇)-Cycloalkyl, -CONR⁴R⁵, -CN oder -XR⁶ steht, wobei

n 0, 1 oder 2 bedeutet;

R³ (C₁-C₁₀)-Alkyl, Hydroxy-(C₁-C₁₀)-alkyl, R⁷R⁸N-(C₁-C₁₀)-alkyl, (C₂-C₂₂)-Alkyl, das durch ein, zwei oder drei Sauerstoffatome unterbrochen ist, (C₃-C₇)-Cycloalkyl, (C₇-C₁₀)-Aralkyl, -(CH₂)_mCOY, Pyridylmethyl, (C₆-C₁₄)-Aryl, 5- bis 14-gliedriges Heteroaryl, (C₆-C₁₄)-Aryl oder 5- bis 14-gliedriges Heteroaryl, die ein oder mehrfach substituiert sind durch einen oder mehrere Gruppen aus der Reihe (C₁-C₅)-Alkyl, (C₃-C₇)-Cycloalkyl, Formyl, (C₁-C₄)-Alkylcarbonyl, Amino, (C₁-C₅)-Alkylamino, Di-(C₁-C₅)-alkylamino, Hydroxy, (C₁-C₅)-Alkoxy, Nitro, Cyano oder Halogen, oder -CH₂CH₂SCOO(C₁-C₄)-Alkyl bedeutet;

25

R⁴ und R⁵ unabhängig voneinander Wasserstoff bedeuten oder wie R³ definiert sind;

30

R⁶ unabhängig von diesem wie R³ definiert ist, wobei -CH₂CH₂SCOO(C₁-C₄)-Alkyl ausgeschlossen ist und wobei, falls X für Schwefel steht, R⁶ zusammen mit R³ eine Ethylengruppe bilden kann;

R⁷ und R⁸ unabhängig voneinander Wasserstoff, (C₁-C₁₀)-Alkyl, (C₇-C₁₀)-Aralkyl oder (C₆-C₁₄)-Aryl, das wie in der Definition von R³ angegeben substituiert sein kann, bedeuten;

35

X Sauerstoff oder Schwefel bedeutet;

Y Hydroxy, (C₁-C₄)-Alkoxy, Amino, (C₁-C₄)-Alkylamino oder Di-(C₁-C₄)-Alkylamino bedeutet; und

m 1, 2 oder 3 bedeutet;

40

sowie deren pharmakologisch annehmbare Salze, wobei, wenn einer der beiden Reste R¹ und R² für Methyl steht, R³ nicht Phenyl oder durch Methyl, Methoxy, Chlor oder Fluor para-substituiertes Phenyl sein kann; wenn einer der beiden Reste R¹ und R² für Methyl steht und n = 0 oder 2 bedeutet, R³ nicht Methyl oder Ethyl sein kann; wenn einer der beiden Reste R¹ und R² für Methyl steht und n = 2 bedeutet, R³ nicht Benzyl sein kann; und wenn einer der beiden Reste R¹ und R² für Ethoxy steht, der andere nicht -SO₂C₆H₅ oder -SO₂C₆H₄-CH₃ sein kann.

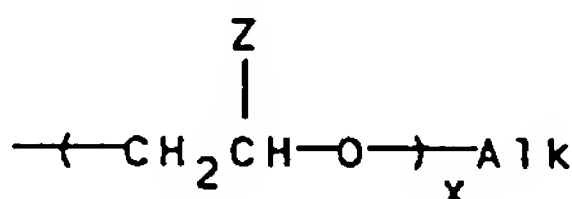
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Alkylgruppen können geradkettig oder verzweigt sein und sind beispielsweise Methyl, Ethyl, n-Propyl, i-Propyl, n-Butyl, sek.-Butyl, i-Butyl, tert.-Butyl, Pentyl, Hexyl, Heptyl, Octyl, Nonyl und Decyl. Bevorzugt haben Alkylgruppen 1 bis 4 Kohlenstoffatome und sind besonders bevorzugt Methyl, Ethyl, n-Propyl, i-Propyl, n-Butyl und tert. Butyl.

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(C₃-C₇)-Cycloalkyl ist bevorzugt Cyclopentyl oder Cyclohexyl. Unter (C₂-C₂₂)-Alkyl, das durch ein, zwei oder drei Sauerstoffatome unterbrochen ist werden beispielsweise Alkoxyalkylgruppen, wie Methoxymethyl, Methoxyethyl, Methoxypropyl, Ethoxymethyl, Ethoxyethyl, Ethoxypropyl, Propoxymethyl, Propoxyethyl und Propoxypropyl, aber auch Polyether, beispielsweise der Formel

55



verstanden, worin

Z Wasserstoff oder Methyl,

x 1, 2 oder 3 und

Alk (C₁-C₆)-Alkyl

5 bedeuten.

(C₇-C₁₀)-Aralkyl ist bevorzugt Benzyl oder Phenethyl. Pyridylmethyl ist beispielsweise Pyrid-2-yl-methyl, Pyrid-3-yl-methyl oder Pyrid-4-yl-methyl. (C₆-C₁₄)-Aryl ist bevorzugt Phenyl. 5- bis 14-gliedriges Heteroaryl enthält als Heteroglieder insbesondere >O, >S,

10



oder >NR⁹,

15 worin R⁹ wie R⁷, aber unabhängig von diesem definiert ist. Sofern der Heterocyclus zwei Heteroglieder aufweist, können diese gleich oder verschieden sein. Ein Stickstoff enthaltender Heterocyclus kann auch über das Stickstoffatom gebunden sein und kann dann neben dem ersten, die Bindung vermittelnden Stickstoffatom noch ein beliebiges der oben genannten Heteroglieder enthalten.

Bevorzugtes Heteroaryl ist 5- oder 6-gliedrig, wobei sich besonders bevorzugte Reste ableiten von 20 Pyrrol, Thiophen, Pyrazol, Imidazol, Oxazol, Isoxazol, Thiazol, Isothiazol, Pyridin, Pyridazin, Pyrimidin und Pyrazin. Die genannten Aryl- und Heteroarylgruppen können ein- oder mehrfach substituiert sein, wobei grundsätzlich jede geeignete Position einen Substituenten tragen kann.

Der Rest -S(O)_nR³ bedeutet bevorzugt

-S(O)_n-(C₁-C₄)-Alkyl, -S(O)_n-Hydroxy-(C₁-C₄)-alkyl,

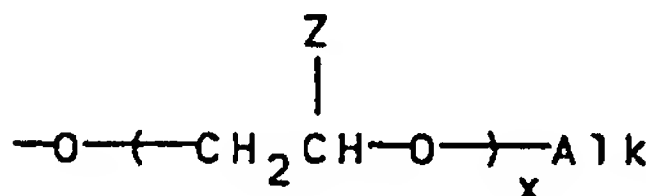
25 -S(O)_n-Cyclohexyl,

-S(O)_nCH₂COY', worin Y' Hydroxy oder (C₁-C₄)-Alkoxy bedeutet,

-S(O)_n-Phenyl oder -S(O)_n-CH₂CH₂SCOO(C₁-C₄)-alkyl. Derjenige der Reste R¹ und R², der nicht für -S(O)-_nR³ steht, bedeutet bevorzugt (C₁-C₄)-Alkyl, -CONHR⁴, worin R⁴ Wasserstoff, (C₁-C₄)-Alkyl oder durch Halogen substituiertes Phenyl bedeutet, -CN, Cyclohexylthio, Phenylthio, (C₁-C₄)-Alkoxy, eine Gruppe der

30 Formel

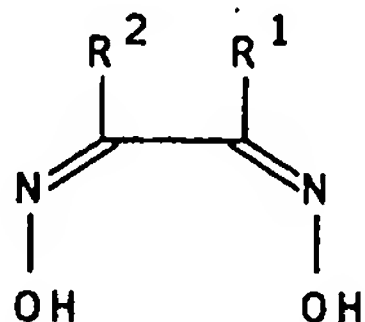
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worin Z, x und Alk wie oben angegeben definiert sind, Pyrid-3-yl-methyloxy, R⁷R⁸-N-(C₁-C₄)-alkoxy, worin R⁷ und R⁸ unabhängig voneinander Methyl oder Benzyl bedeuten, oder SCH₂COY', worin Y' wie oben 40 angegeben definiert ist.

Die Verbindungen der allgemeinen Formel I können beispielsweise dadurch hergestellt werden, daß eine Verbindung der allgemeinen Formel II

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(II)

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worin einer der Reste R¹ und R² für -SR³ und der andere für (C₁-C₁₀)-Alkyl, (C₃-C₇)-Cycloalkyl, -CONR⁴R⁵, -CN oder -XR⁶ steht, wobei R³, R⁴, R⁵, R⁶ und X wie oben angegeben definiert sind, oxidiert wird und gegebenenfalls die so erhaltene Verbindung der allgemeinen Formel I, worin n=0 ist, zur entsprechenden 55 Verbindung der allgemeinen Formel I, worin n=1 oder 2 ist, weiteroxidiert wird.

Zur Oxidation einer Verbindung der allgemeinen Formel II zu einer Verbindung der allgemeinen Formel I, worin n=0 ist, können herkömmliche Reagentien wie zum Beispiel Halogene, N-Chlor- und N-Bromsuccinimid, Alkali- und Erdalkalihypochlorite, Alkylhypochlorite, wie z.B. tert. Butylhypochlorit, Blei-(IV)-Verbin-

dungen, wie z.B. Bleitetraacetat, Eisen-(III)-Salze, wie z.B. rotes Blutlaugensalz, oder nitrose Gase, wie z.B. N_2O_3 oder N_2O_4 verwendet werden. Ein bevorzugtes Oxidationsmittel ist dabei N_2O_4 .

Die Umsetzung wird bevorzugt in einem Lösungsmittel, wie beispielsweise Wasser, einem Alkohol, einem Ether, Essigester, Methylenchlorid, Cyclohexan, DMF, DMSO, Benzol, Toluol oder Chlorbenzol bei Temperaturen von -10°C bis 50°C , vorzugsweise von -5°C bis 25°C ausgeführt. Ein besonders bevorzugtes Lösungsmittel ist Diethylether.

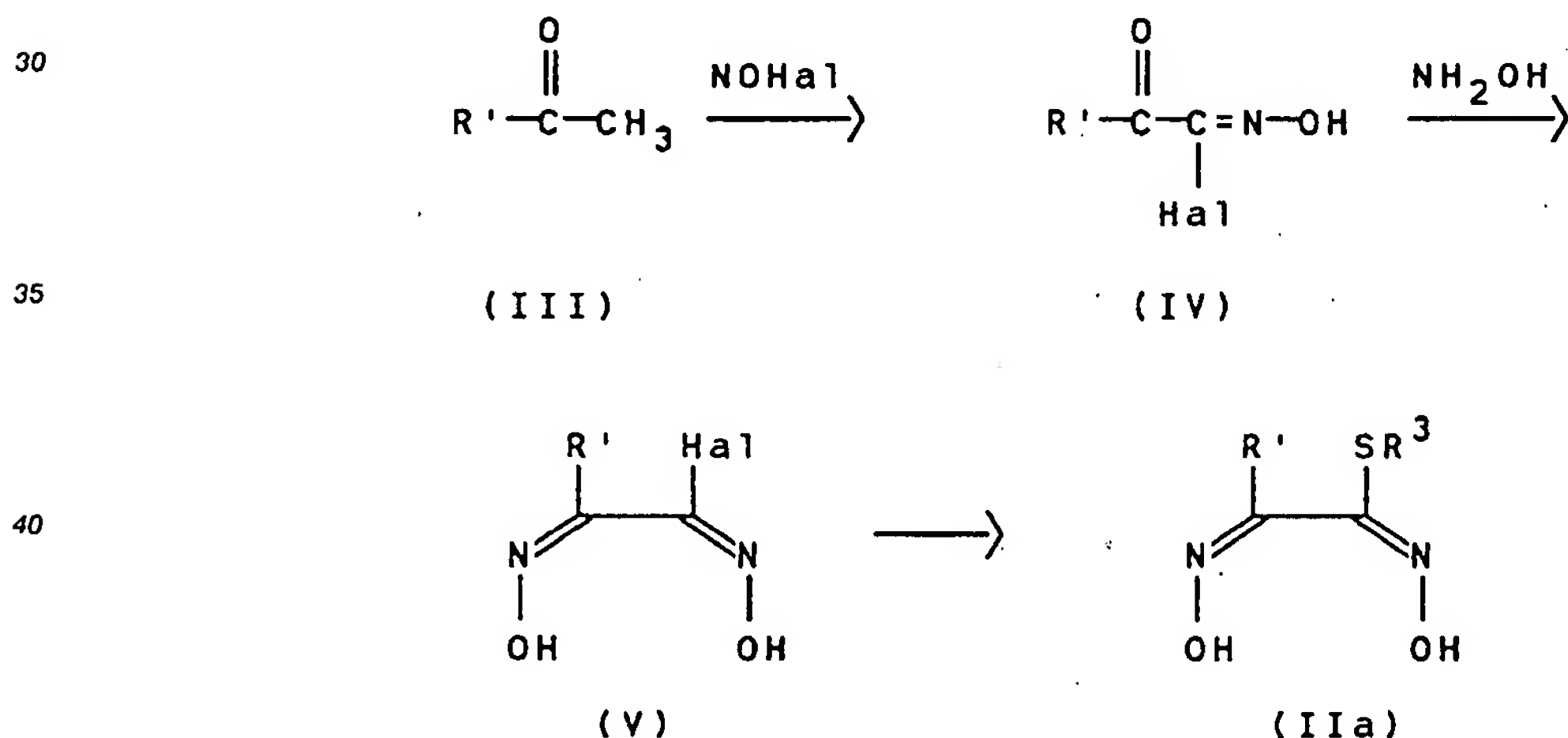
Oxidationsmittel, die zur Umsetzung von Verbindungen der allgemeinen Formel I, in denen $n=0$ ist, zu Verbindungen der allgemeinen Formel I, in denen $n=1$ oder 2 ist, geeignet sind, sind beispielsweise Wasserstoffperoxid in essig- oder trifluoressigsäurem Medium, sowie Persäuren, vorzugsweise m-Chlorperbenzoesäure, die in einem organischen Lösungsmittel, insbesondere Methylenchlorid oder Aceton, eingesetzt werden. Die Temperatur liegt bei dieser Umsetzung bevorzugt bei -10 bis 50°C , besonders bevorzugt bei 20 bis 30°C .

Werden äquimolare Mengen Oxidationsmittel eingesetzt, so entstehen Verbindungen der allgemeinen Formel I, in denen $n=1$ bedeutet, während die Verwendung überschüssigen Oxidationsmittels unter den gleichen Bedingungen, ohne die Notwendigkeit einer Isolierung der Zwischenstufe, zu Verbindungen der allgemeinen Formel I, in denen $n=2$ bedeutet, führt.

Bei der Oxidation der Verbindungen der allgemeinen Formel II fallen in der Regel die Verbindungen der allgemeinen Formel I in Form von Isomerengemischen an. Diese lassen sich aber durch bekannte Methoden wie Umkristallisieren oder chromatographische Methoden, insbesondere Säulenchromatographie, trennen. Isomerengemische werden auch erhalten, wenn ein reines Isomeres in Substanz oder in einem inerten Lösungsmittel gelöst auf Temperaturen von 50 bis 200°C erhitzt oder bei 0 bis 50°C photolysiert wird. Durch Trennung des so erhaltenen Gemisches ist es somit möglich, ein Isomeres in das andere umzuwandeln.

Die Verbindungen der allgemeinen Formel II sind literaturbekannt oder können in Analogie zu bekannten Verfahren hergestellt werden.

Beispielsweise kann nach folgendem Schema vorgegangen werden:



In den allgemeinen Formeln III bis IIa bedeuten dabei R' (C_1 - C_{10})-Alkyl, (C_3 - C_7)-Cycloalkyl, $-\text{CONR}^4\text{R}^5$, $-\text{CN}$ oder XR^6 , wobei R^3 , R^4 , R^5 und R^6 wie oben angegeben definiert sind, und Hal Halogen, insbesondere Chlor.

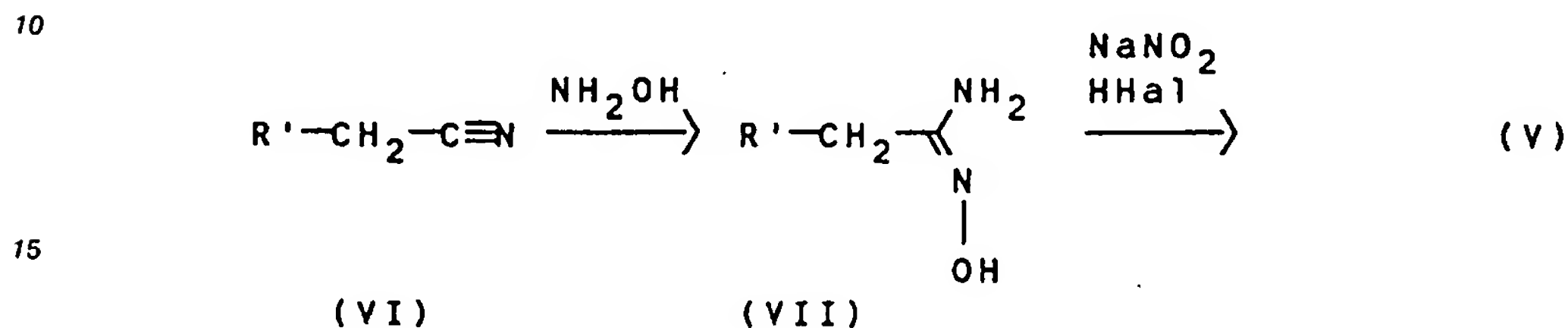
Die Umsetzung der Verbindung der allgemeinen Formel III mit z.B. Nitrosylchlorid wird beispielsweise in Tetrachlorkohlenstoff oder, bevorzugt, in Ether bei 0 bis 20°C ausgeführt. Die anschließende Oximierung mit Hydroxylamin erfolgt in alkoholischer oder bevorzugt wäßriger Lösung (Liebigs Ann. Chem. 44, 113 (1925), Tetrahedron 19, 143 (1963)).

Die Hydroximinoylhalogenide der allgemeinen Formel V werden anschließend mit einem Thiol HSR^3 zur Verbindung der Formel IIa umgesetzt. Bevorzugt wird dabei die Verbindung der allgemeinen Formel V in einem organischen Lösungsmittel, beispielsweise einem niederen Alkohol, Ether oder Ester, bevorzugt aber in Diethylether, vorgelegt, eine Hilfsbase, beispielsweise Alkoholat, anorganisches Carbonat oder Hydroxid oder ein tertiäres Amin, bevorzugt Triethylamin, in 10 bis 15 mol%igem Überschuß zugegeben und das

Thiol in 5 bis 10 mol%igem Überschuß zugetropft. Die Temperatur liegt dabei bevorzugt bei 0 bis 60°C, besonders bevorzugt 20 bis 40°C.

In einer alternativen Vorgehensweise kann die Verbindung der allgemeinen Formel IV auch zuerst mit dem Thiol HSR^3 und anschließend mit Hydroxylamin umgesetzt werden, wobei die oben angegebenen Reaktionsbedingungen auch in diesem Falle anzuwenden sind.

Die Verbindungen der allgemeinen Formel V können darüberhinaus auch nach folgendem Schema erhalten werden:



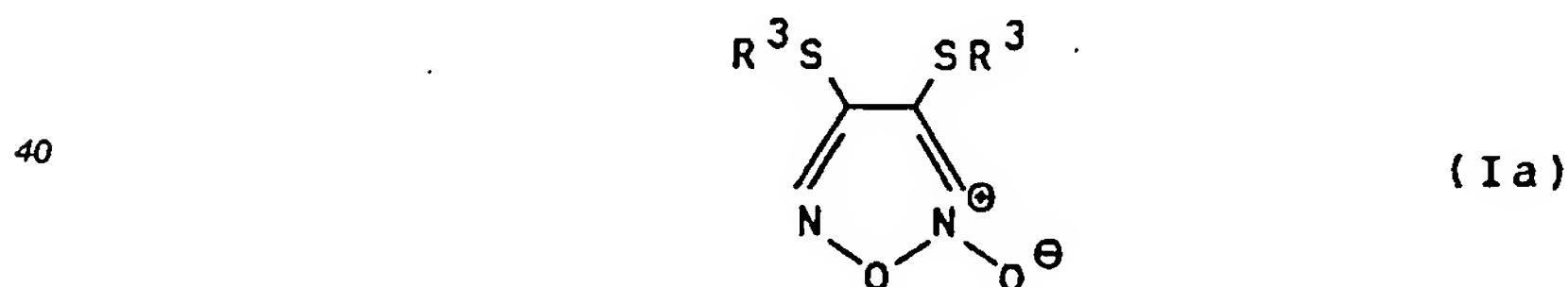
Die Nitrile der allgemeinen Formel VI können dabei in die Amidoxime der allgemeinen Formel VII überführt werden (Chem. Heterocycl. Compd. 1985, 988), deren Nitrosierung in 10 - 60%iger Mineralsäure HHal zu den Verbindungen der allgemeinen Formel V führt (Synth. Commun. 22, 453 (1992)). Sollen Verbindungen der allgemeinen Formel I, in denen einer der beiden Reste R^1 und R^2 für $-\text{CONR}^4\text{R}^5$ steht, hergestellt werden, so können die entsprechenden Nitrile der allgemeinen Formel VIa



durch Aminierung von Cyanessigsäureestern erhalten werden (Aust. J. Chem. 29, 1039 (1976)).

Erfindungsgemäße Verbindungen der allgemeinen Formel I, in denen einer der Reste R^1 und R^2 für CONH_2 steht, können durch alkalische Verseifung entsprechender Nitrile erhalten werden. Diese Umsetzung wird bevorzugt in einem Lösungsmittel, insbesondere Wasser, unter Zusatz von Alkalimetallhydroxiden und Zugabe von Wasserstoffperoxid durchgeführt. Die Temperatur liegt dabei bevorzugt bei 0 bis 50°C.

Erfindungsgemäße Verbindungen der allgemeinen Formel Ia

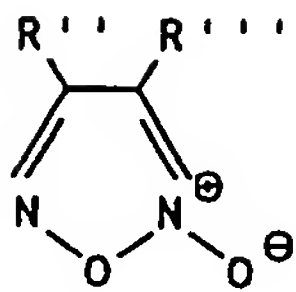


worin R^3 wie oben angegeben definiert ist, können durch basenkatalysierte Umsetzung von Dichlorglyoxim mit Thiolen R^3SH oder Thioglykol und nachfolgender Oxidation erhalten werden.

Bei der Umsetzung mit den Thiolen R^3SH werden 2 Moläquivalente pro Mol Dichlorglyoxim verwendet, bei der Umsetzung mit Thioglykol werden die Reaktionspartner im Molverhältnis 1:1 eingesetzt.

Die Reaktion wird im allgemeinen in Gegenwart einer Base, vorzugsweise in stöchiometrischen Mengen, durchgeführt, wobei Alkalimetallalkoholate, wie Natriummethanolat, Alkalimetallhydroxide oder -carbonate, wie Kaliumcarbonat oder Trialkylamine, wie Triethylamin, besonders bevorzugt sind.

Die Verbindungen der allgemeinen Formel Ia können durch Oxidation zu den entsprechenden Bissulfonylfuroxanen und anschließenden sequentiellen Austausch der Sulfonylreste zu erfindungsgemäßen Verbindungen der allgemeinen Formel Ib



(Ib)

5

worin R'' - XR^6 und R''' - SO_2R^3 oder - SR^3 bedeuten, umgesetzt werden. Dazu werden die genannten Bissulfonylfuroxane, die wie oben angegeben oder nach sonstigen literaturbekannten Verfahren (z.B. J.Heterocyclic Chem. 14, 1415 (1977)) hergestellt sein können, in einem Lösungsmittel, beispielsweise einem Alkohol, Wasser oder Aceton, gelöst und unter Zusatz einer Base, beispielsweise Natriumhydroxid, Natriumalkoholat oder einem Alkalicarbonat, mit einem Alkohol HOR^6 oder einem Mercaptan HSR^6 umgesetzt. Hierbei wird selektiv nur die 4-Sulfonylgruppe ausgetauscht. Gewünschtenfalls kann anschließend auch die 3-Sulfonylgruppe durch erneute Umsetzung mit einem Mercaptan HSR^6 ausgetauscht werden.

Erfindungsgemäße Verbindungen der allgemeinen Formel I, die eine basische Gruppe enthalten, können mit anorganischen oder organischen Säuren Salze bilden. Geeignete Säuren für die Bildung pharmakologisch annehmbarer Säureadditionssalze sind beispielsweise: Chlorwasserstoff, Bromwasserstoff, Naphthalindisulfonsäuren, insbesondere Naphthalindisulfonsäure(1,5), Phosphor-, Salpeter-, Schwefel-, Oxal-, Milch-, Wein-, Essig-, Salicyl-, Benzoe-, Ameisen-, Propion-, Pivalin-, Diethylessig-, Malon-, Bernstein-, Pimelin-, Fumar-, Malein-, Apfel-, Sulfamin-, Phenylpropion-, Glucon-, Ascorbin-, Isonicotin-, Methansulfon-, p-Toluolsulfon-, Zitronen- oder Adipinsäure. Die Säureadditionssalze können wie üblich durch Vereinigung der Komponenten, zweckmäßigerweise in einem geeigneten Lösungs- oder Verdünnungsmittel, hergestellt werden. Erfindungsgemäße Verbindungen, die eine saure Gruppe enthalten, können mit anorganischen oder organischen Basen Salze bilden, beispielsweise Natrium- oder Kaliumsalze.

Die Verbindungen der allgemeinen Formel I und ihre pharmakologisch annehmbaren Salze besitzen wertvolle pharmakologische Eigenschaften. Am Modell der Kalium-depolarisierten Pulmonalarterie des Meerschweinchen (Godfraind and Kaba (Arch.Int.Pharmacodyn.Ther. 196, (Suppl) 35 bis 49, 1972) führen sie in niedrigen Konzentrationen zu einer lang anhaltenden Relaxation. Diese Wirkung kann mit Oxyhämoglobin inhibiert werden, was auf einen NO-medierten Mechanismus deutet. Stickstoffmonoxid führt als Aktivator der Guanylatcyclase zu einer Erhöhung von cyclischem Guanosinmonophosphat, welches im glatten Muskel eine Relaxation und in den Blutplättchen antiadhäsive und antiaggregatorische Wirkungen verursacht. Stickstoffmonoxid ist außerdem auch entscheidend beteiligt bei Lernvorgängen, bei der Regulation der Nierenfunktion, bei der Immunabwehr, beim septischen Schock und bei erektilen Dysfunktionen. Die erfindungsgemäßen Verbindungen können somit bei den genannten Indikationen eingesetzt werden.

Vor allem aber haben sich NO-Donoren zur Behandlung und Prophylaxe von angina pectoris bewährt.

Die Verbindungen der allgemeinen Formel I und ihre pharmakologisch annehmbaren Salze können daher am Menschen als Heilmittel für sich allein, in Mischungen untereinander oder in Form von pharmazeutischen Zubereitungen verabreicht werden, die eine enterale oder parenterale Anwendung gestatten und die als aktiven Bestandteil eine wirksame Dosis mindestens einer Verbindung der allgemeinen Formel I oder eines Salzes davon, neben üblichen pharmazeutisch einwandfreien Träger- und Zusatzstoffen enthalten.

Die Heilmittel können oral, z.B. in Form von Pillen, Tabletten, Lacktabletten, Dragees, Hart- und Weichgelatine kapseln, Lösungen, Sirupen, Emulsionen oder Suspensionen oder Aerosolmischungen verabreicht werden. Die Verabreichung kann aber auch rektal, z.B. in Form von Suppositorien, oder parenteral, z.B. in Form von Injektionslösungen, oder perkutan, z.B. in Form von Salben, elastischen Flüssigpflastern, transdermalen Systemen oder Tinkturen, erfolgen.

Zur Herstellung der pharmazeutischen Präparate können pharmazeutisch inerte anorganische oder organische Trägerstoffe verwendet werden. Für die Herstellung von Pillen, Tabletten, Dragees und Hartgelatine kapseln kann man z.B. Lactose, Maisstärke oder Derivate davon, Talk, Stearinsäure oder deren Salze etc. verwenden. Trägerstoffe für Weichgelatine kapseln und Suppositorien sind z.B. Fette, Wachse, halb feste und flüssige Polyole, natürliche oder gehärtete Öle etc. Als Trägerstoffe für die Herstellung von Lösungen und Sirupen eignen sich z.B. Wasser, Saccharose, Invertzucker, Glukose, Polyole etc. Als Trägerstoffe für die Herstellung von Injektionslösungen eignen sich z.B. Wasser, Alkohole, Glycerin, Polyole oder pflanzliche Öle.

Die pharmazeutischen Präparate können neben den Wirk- und Trägerstoffen noch Zusatzstoffe, wie z.B. Füllstoffe, Streck-, Spreng-, Binde-, Gleit-, Netz-, Stabilisierungs-, Emulgier-, Konservierungs-, Süß-, Färbe-, Geschmacks- oder Aromatisierungs-Mittel, Puffersubstanzen, ferner Lösungsmittel oder Lösungsvermittler oder Mittel zur Erzielung eines Depoteffekts, sowie Salze zur Veränderung des osmotischen

Drucks, Überzugsmittel oder Antioxidantien enthalten. Sie können auch zwei oder mehrere Verbindungen der allgemeinen Formel I oder ihrer pharmakologisch annehmbaren Salze und noch andere therapeutisch wirksame Stoffe enthalten.

Derartige andere therapeutisch wirksame Substanzen sind beispielsweise: β -Rezeptorenblocker, wie z.B. Propranolol, Pindolol, Metoprolol; Vasodilatoren, wie z.B. Carbocromen; Beruhigungsmittel, wie z.B. Barbitursäurederivate, 1,4-Benzodiazepine und Meprobamat; Diuretica, wie z.B. Chlorothiazid; das Herz tonisierende Mittel, wie z.B. Digitalispräparate; blutdrucksenkende Mittel, wie z.B. Hydralazin, Dihydralazin, Ramipril, Prazosin, Clonidin, Rauwolfia-Alkaloide; Mittel, die den Fettsäurespiegel im Blut senken, wie z.B. Bezafibrat, Fenofibrat; Mittel für die Thromboseprophylaxe, wie z.B. Phenprocoumon.

Die Verbindungen der allgemeinen Formel I, ihre pharmakologisch annehmbaren Salze und pharmazeutische Präparate, welche die Verbindungen der allgemeinen Formel I oder ihre pharmakologisch annehmbaren Salze als Wirkstoffe enthalten, können am Menschen bei der Bekämpfung bzw. Vorbeugung von Erkrankungen des kardiovaskulären Systems verwendet werden, beispielsweise als antihypertensive Heilmittel bei den verschiedenen Formen des Bluthochdrucks, bei der Bekämpfung bzw. Vorbeugung von Angina pectoris usw. Darüberhinaus können sie auch zur Behandlung erektiler Dysfunktionen eingesetzt werden. Die Dosierung kann innerhalb weiter Grenzen variieren und ist in jedem einzelnen Fall den individuellen Gegebenheiten anzupassen. Im allgemeinen ist bei oraler Verabreichung pro menschlichem Individuum eine Tagesdosis von etwa 0,5 bis 100 mg, vorzugsweise 1 bis 20 mg, angemessen. Auch bei anderen Applikationsformen liegt die Tagesdosis, wegen der guten Resorption der Wirkstoffe, in ähnlichen Mengenbereichen, d.h. im allgemeinen ebenfalls bei 0,5 bis 100 mg/Mensch. Die Tagesdosis wird normalerweise in mehrere, z. B. 2 bis 4 Teilverabreichungen aufgeteilt.

Beispiel 1

N-Isopropyl-3-phenylmercapto-furoxan-4-carbonamid

a) 3-Amino-3-hydroximino-N-isopropylpropionamid

Eine Lösung von 93,6 g (0,9 mol) Natriumcarbonat in 240 ml Wasser wird mit einer Lösung von 61,3 g (0,9 mol) Hydroxylaminhydrochlorid versetzt, eine halbe Stunde gerührt und mit 100 ml Ethanol versetzt.

Die so erhaltene Lösung wird zu einer Lösung von 87 g (0,7 mol) Cyano-N-isopropylacetamid gegeben und 1h auf 70°C erhitzt. Nach Stehen über Nacht wird vom Niederschlag abgesaugt, eingeeengt, der Rückstand mit 200 ml Wasser verrieben, erneut abgesaugt und der verbleibende Rückstand aus Ethanol umkristallisiert.

Man erhält 69,9 g (63%) 3-Amino-3-hydroximino-N-isopropylpropionamid

Fp.: 135°C

b) 3-Chlor-2,3-bis-hydroximino-N-isopropylpropionamid

115 g (0,72 mol) 3-Amino-3-hydroximino-N-isopropylpropionamid werden in 1320 ml konz. HCl gelöst, auf 0°C gekühlt und eine Lösung von 149 g (2,16 mol) Natriumnitrit in 360 ml Wasser so zugetropft, daß die Temperatur 5°C nicht überschreitet. Zur Aufarbeitung wird abgesaugt, in 2000 ml Essigester suspendiert, mit 500 ml H₂O ausgerührt und die organische Phase nach Trocknen über Na₂SO₄ eingeeengt.

Man erhält 28 g (18%) 3-Chlor-2,3-bis-hydroximino-N-isopropylpropionamid.

Das Produkt schmilzt unter Zersetzung

¹H-NMR: 1,04 (d, 6H, CH₃), 3,94 (oct, 1H, CH-N), 8,17 (d, 1H, NH), 12,08 (s, 1H, OH), 12,80 (s, 1H, OH)

c) 2,3-Bis-hydroximino-N-isopropyl-3-phenylmercapto-propionamid

22,8 g (0,11 mol) 3-Chlor-2,3-bis-hydroximino-N-isopropylpropionamid und 13,3 g (0,12 mol) Thiophenol werden in 1000 ml Diethylether vorgelegt und eine Lösung von 12,6 g (0,12 mol) Triethylamin in 100 ml Diethylether zugetropft.

Nach 1h Rühren bei RT wird nacheinander mit 1N H₂SO₄, gesättigter Natriumcarbonat-Lösung und Wasser gewaschen, mit MgSO₄ getrocknet und eingeeengt, der Rückstand mit Hexan/Diethylether verrieben und abgesaugt.

Man erhält 21,1 g (68%) 2,3-Bis-hydroximino-N-isopropyl-3-phenylmercapto-propionamid

Fp.: 148,5°C

d) N-Isopropyl-3-phenylmercapto-furoxan-4-carbonamid

21 g (75 mmol) 2,3-Bis-hydroximino-N-isopropyl-3-phenylmercapto-propionamid werden in 500 ml Diethylether suspendiert und 8,24 g (90 mmol) Distickstofftetroxid bei 0°C zugetropft.

Nach 1h bei 0°C wird auf Eis-Wasser gegeben, die etherische Phase abgetrennt, getrocknet, eingeeengt und der Rückstand aus Hexan/Ether 1:1 umkristallisiert.

Man erhält 14,6 g (70%) N-Isopropyl-3-phenylmercaptofuroxan-4-carbonamid
Fp.: 81°C

Beispiel 2

5

4-Phenylmercapto-furoxan-3-carbonitril

12,6 g (57 mmol) 2,3-Bishydroximino-3-phenylmercapto-propionitril werden in 600 ml Diethylether vorgelegt und bei 0°C 6,3 g (68 mmol) Distickstofftetroxid zugetropft. Nach 3h bei 0°C wird auf Eis-Wasser
10 gegeben, die etherische Phase abgetrennt, getrocknet und eingeeengt. Der Rückstand wird an Kieselgel mit Essigester : Hexan = 1:1 chromatographiert und die Hauptfraktion aus Ether/Hexan = 1:1 umkristallisiert.
Man erhält 6,12 g (49%) 4-Phenylmercapto-furoxan-3-carbonitril
Fp.: 59,5°C

15 Beispiel 3

4-Phenylsulfinyl-furoxan-3-carbonitril und 4-Phenylsulfonyl-furoxan-3-carbonitril

2 g (9,7 mmol) 4-Phenylmercaptofuroxan-3-carbonitril werden in 20 ml Aceton gelöst und eine zuvor mit
20 6 g Na₂SO₄ getrocknete Lösung von 7 g (~ 32,5 mmol) ca. 80%iger m-Chlorperbenzoesäure so weit zugetropft bis unter stetiger DC-Kontrolle der gewünschte Umsetzungsgrad eingestellt ist.
Zur Aufarbeitung wird auf Eis-Wasser gegossen, mit Methylenchlorid extrahiert und die organische Phase mehrfach mit Bicarbonat-Lösung, Natriumsulfatlösung und Wasser gewaschen. Der nach Trocknen und Einrotieren verbleibende Rückstand wird an Kieselgel mit CH₂Cl₂ : Hexan = 1:1 chromatographiert und die
25 jeweilige Hauptfraktion aus Ether : Hexan umkristallisiert.
4-Phenylsulfinylfuroxan-3-carbonitril Fp.: 81°C
4-Phenylsulfonylfuroxan-3-carbonitril Fp.: 82°C

Beispiel 4

30

4-Phenylmercaptofuroxan-3-carbonamid

1,12 g (5,1 mmol) 4-Phenylmercaptofuroxan-3-carbonitril werden in 15 ml 2N NaOH suspendiert und
1,81 g (5,25 mmol) 10%ige Wasserstoffperoxidlösung zugetropft. Nach 4h bei RT wird abgesaugt und aus
35 Isopropanol umkristallisiert.
Man erhält 0,7 g (58%) 4-Phenylmercaptofuroxan-3-carbonamid
Fp.: 139 - 140°C

Beispiel 5

40

4-(β-(Methoxycarbonylmercapto)-ethylmercapto)-3-methylfuroxan

a) 1-(2-(Methoxycarbonylmercapto)-ethylmercapto)-2-methyl-glyoxim
20,0 g (0,15 mol) 1-Chlor-2-methyl-glyoxim werden zusammen mit 24,5 g (0,16 mol) β-Mercaptoethylthiokohlensäuremethylester in 1500 ml Diethylether und 16,75 g (0,16 mol) Triethylamin in 60 ml Ether
45 zugetropft. Es wird 18h bei RT gerührt und 2h unter Rückfluß erhitzt.
Zur Aufarbeitung wird abgesaugt, die Ether-Phase mit Wasser gewaschen, getrocknet, eingeeengt und aus Isopropanol umkristallisiert.
Man erhält 12,3 g (33%) 1-(2-Methoxycarbonylmercapto)-ethylmercapto)-2-methyl-glyoxim
50 Fp.: 147 - 151°C
b) 4-(β-(Methoxycarbonylmercapto)-ethylmercapto)-3-methylfuroxan
12,3 g (48,8 mmol) β-Methoxycarbonylmercapto-ethylmercapto-methyl-glyoxim werden in 340 ml Diethylether gelöst und bei 0°C 5,4 g (58,5 mmol) Distickstofftetroxid zugetropft. Nach 18h bei RT wird eingeeengt, in Methylenchlorid aufgenommen, mit H₂O gewaschen, getrocknet, eingeeengt und der
55 Rückstand an Kieselgel mit Hexan : Essigester = 3:2 chromatographiert.
Man erhält 9,9 g (81%) 4-(β-(Methoxycarbonylmercapto)-ethylmercapto)-3-methyl-furoxan als farbloses, viskoses Öl.
¹H-NMR: 2,08 (s, 3H, CH₃), 3,25 (t, 2H, α-CH₂), 3,45 (t, 2H, β-CH₂), 3,80 (s, 3H, CH₂O)

Beispiel 6**3-Methoxycarbonylmethylmercapto-4-methyl-furoxan**

5 3,8 g (18,6 mmol) 4-Methoxycarbonylmethylmercapto-3-methyl-furoxan (Beispiel 9) werden unter N₂ in 50 ml Xylol 4h auf 140°C erhitzt. Zur Aufarbeitung wird eingeeengt und an Kieselgel mit Hexan : Essigester 3:1 chromatographiert.

Man erhält 0,85 g (22%) 3-Methoxycarbonylmethylmercapto-4-methyl-furoxan

Öl, ¹H-NMR: 2,38 (s, 3H, CH₃), 3,62 (s, 3H, CH₃O), 4,82 (s, 2H, CH₂)

10 Analog den vorstehenden vorschritten können hergestellt werden:

Beispiel 7**4-(β-Hydroxyethylmercapto)-3-methylfuroxan**

15

Öl, ¹H-NMR: 2,08 (s, 1H, CH₃) 3,27 (t, 2H, H-α) 3,72 (q, 2H, H-β) 5,20 (t, 1H, OH)

Vorstufe: 1-(β-Hydroxyethylmercapto)-2-methyl-glyoxim Fp.: 129°C

Beispiel 8

20

4-((β-Methoxycarbonylmercapto)-ethylsulfinyl)-3-methylfuroxan

Öl, ¹H-NMR: 2,24 (s, 1H, CH₃) 3,25-3,40 (m, 2H, H-β) 3,55-3,75 (m, 2H-H-α) 3,80 (s, 3H, CH₃O)

Beispiel 9**4-Methoxycarbonylmethylmercapto-3-methyl-furoxan**

Fp.: 49°C

30 Vorstufe: 1-Methoxycarbonylmethylmercapto-2-methylglyoxim

Fp.: 121 - 126°C (d)

¹H-NMR: 1,95 (s, 3H, CH₃) 3,61 (s, 3H, OCH₃) 3,88 (s, 2H, CH₂) 11,58 (s, 1H, OH) 12,01 (s, 1H, OH)

Beispiel 10

35

4-Methoxycarbonylmethylsulfinyl-3-methyl-furoxan

Öl, ¹H-NMR: 2,13 (s, 3H, CH₃) 3,77 (s, 3H, CH₃O) 4,59 (AB-d, 2H, CH₂)

Beispiel 11**S-(3-Methylfuroxan-4-yl)-mercaptoessigsäure**

Fp.: 106 - 108°C

45

Beispiel 12**3-Phenylmercaptofuroxan-4-p-chlorcarbonanilid**

50 Fp.: 159 - 160°C

Vorstufe:

2,3-Bishydroximino-3-phenylmercapto-p-chlorpropionanilid

Fp.: 148°C

55

Beispiel 13

4-Butylmercapto-furoxan-3-carbonamid

5 Fp.: 95°C

Beispiel 14

3-((β -Methoxycarbonylmercapto)-ethylmercapto)-furoxan-4-p-chlorcarbonanilid

10

Fp.: 97 - 100°C

Beispiel 15

15 **3- β -Hydroxyethylmercapto-N-isopropyl-furoxan-4-carbonamid**

Öl, ¹H-NMR: 1,20 (d, 6H, CH₃) 3,12 - 3,20 und 3,55-3,65 (m, 4H, CH₂), 4,10 (oct, 1H, CH-N), 5,05 (bs, 1H, OH), 9,00 (d, 1H, NH)

Vorstufe:

20 **3-(β -Hydroxyethylmercapto)-2,3-bishydroximino-N-isopropylpropionamid**

Öl, ¹H-NMR: 1,10 (d, 6H, H iprop-CH₃), 3,11 (t, 2H, H- α) 3,52 (q, 2H, H- β), 3,90 (oct, 1H, i-propCH), 8,10 (d, 1H, NH), 11,79 (s, 1H, OH) 12,17 (s, 1H, OH)

Beispiel 16

25

3-Butylmercapto-N-isopropyl-furoxan-4-carbonamid

Öl, ¹H-NMR: 0,85 (t, 3H, Butyl-4), 1,16 (d, 6H, ipropCH₃) 1,35 (sext, 2H, Butyl-3), 1,46 (quint., 2H, Butyl-2), 3,04 (t, 2H, Butyl-1), 4,06 (oct, 1H, iprop-CH), 9,03 (d, 1H, NH)

30 Vorstufe:

3-Butylmercapto-2,3-bishydroximino-N-isopropyl-propionamid

Öl, ¹H-NMR: 0,89 (t, 3H, Butyl-4), 1,08 (d, 6H, ipropCH₃), 1,37 (sext, 2H, Butyl-3), 1,46 (quart, 2H, Butyl-2), 3,05 (t, 2H, Butyl-1), 3,95 (okt, 1H, iprop-CH), 8,12 (d, 1H, NH), 11,55 (s, 1H, OH), 12,26 (s, 1H, OH)

35 **Beispiel 17**

4-Butylmercapto-furoxan-3-carbonitril

Öl, ¹H-NMR: 0,91 (t, 3H, Butyl-4), 1,43 (sext. 2H, Butyl-3), 1,73 (quint, 2H, Butyl-2), 3,25 (t, 2H, Butyl-1)

40

Beispiel 18

3-Butylmercapto-furoxan-4-carbonitril

45 Öl, ¹H-NMR: 0,88 (t, 3H, Butyl-4) 1,35 (sext, 2H, Butyl-3), 1,58 (q, 2H, Butyl-2), 3,04 (t, 2H, Butyl-1)

Beispiel 19

3-Butylsulfonyl-furoxan-4-carbonitril

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Öl, ¹H-NMR: 0,90 (t, 3H, Butyl-4), 1,45 (sext., 2H, Butyl-3), 1,75 (quint, 2H, Butyl-2), 3,73 - 3,81 (m, 2H, Butyl-1)

55

Beispiel 20**1,2,5-Oxadiazolo[3,4-b][1,4]dithian-N-oxid**

- 5 a) Zu einer Lösung von 9,4 g (60 mmol) Dichlorglyoxim (Tetrahedron 19 (1963) 143) und 5,65 g (60 mmol) Dithioglykol in 120 ml Methanol werden bei -40°C 21,6 g (120 mmol) einer 30%igen Natriummethanolatlösung langsam zugetropft. Man läßt innerhalb von 3h auf Raumtemperatur erwärmen, rührt noch 2h nach und engt dann komplett ein.
- Man verrührt den Rückstand mit 40 ml Wasser, saugt ab und erhält 9,3 g (87%) 2,3-Bishydroxyimino-
 10 1,4-dithian.
 Fp.: 202 - 205°C
- b) Zu einer Lösung von 9,3 g 2,3-Bishydroxyimino-1,4-dithian in 330 ml 10%iger Natronlauge werden bei 0°C 330 ml 14% Natriumhypochloritlösung zugetropft. Der ausgefallene Niederschlag wird sofort abgesaugt, mit Wasser gewaschen und im Vakuum getrocknet. Man erhält 6,5 g (71%) [1,2,5]-
 15 Oxadiazolo[3,4-b][1,4]dithian-N-oxid,
 Fp.: 78 - 79°C

Beispiel 21**3,4-Biscyclohexylmercapto-furoxan**

- a) Zu einer Lösung von 11,8 g (75 mmol) Dichlorglyoxim und 15 g (150 mmol) Cyclohexylmercaptan in 150 ml Methanol werden bei -40°C 27 g (150 mmol) einer 30%igen Natriummethanolatlösung langsam zugetropft. Man läßt innerhalb von 3h auf Raumtemperatur erwärmen, rührt über Nacht und saugt den gebildeten Niederschlag ab. Das Filtrat wird im Vakuum eingeeengt, der Rückstand in 60 ml heißem
 25 Isopropanol gelöst und das Produkt durch Zugabe von 500 ml Petrolether ausgefällt. Man erhält 15,2 g (64%) Biscyclohexylmercaptoglyoxim.
 Fp.: 160 - 161°C
- b) Zu einer Lösung von 6,3 g Biscyclohexylmercaptoglyoxim in 125 ml 10%iger Natronlauge tropft man bei 0°C 125 ml 14% Natriumhypochloritlösung zu. Das ölig ausgefallene Produkt wird mit Essigester extrahiert und durch Chromatographie mit Cyclohexan/Essigester 90 : 5 gereinigt. Nach anschließender Umkristallisation aus Isopropanol erhält man 1,5 g 3,4-Biscyclohexylmercapto-furoxan.
 30 Fp.: 80 - 81°C

Beispiel 22**3,4-Bisphenylmercapto-furoxan**

- Aus Dichlorglyoxim und Thiophenol wird analog Beispiel 21 3,4-Bisphenylmercapto-furoxan erhalten als leicht gelbliches Öl, das auch nach chromatographischer Reinigung nicht kristallisiert. Als Strukturbeweis wird das Produkt durch Oxidation mit Wasserstoffperoxid in Eisessig in das bekannte 3,4-Bisphenylsulfonyl-
 40 1,2,5-oxa-diazol-2-oxid,
 Fp.: 155°C, überführt.

Beispiel 23**4-(2-Methoxyethyloxy)-3-phenylsulfonylfuroxan**

- Eine Lösung von 6,0 g 3,4-Diphenylsulfonylfuroxan in 70 ml Aceton wird mit einer Lösung von 3,7 g Glykolmonomethylether in 26 ml Aceton sowie 1,0 g Natriumhydroxid in 8 ml Wasser versetzt, wobei sich die Reaktionsmischung auf 40°C erwärmt. Nach 1h kühlt man auf 10°C ab, filtriert vom ausgefallenen Natriumphenylsulfinat ab und engt das Filtrat ein. Der Rückstand wird mit 500 ml Essigester verrührt und erneut abfiltriert. Das Filtrat wird eingeeengt, aus 30 ml Ethanol umkristallisiert, und man erhält 3,4 g (68%)
 50 4-(2-Methoxyethyloxy)-3-phenylsulfonylfuroxan.
 55 Fp.: 105 - 107°C

Beispiel 24**4-Methoxy-3-phenylsulfonylfuroxan**

5 Analog Beispiel 23 wurde 4-Methoxy-3-phenylsulfonylfuroxan in 80% Ausbeute erhalten.

Fp.: 109 - 111°C

¹³C-NMR: δ = 58.3, 110.7, 128.3, 130.0, 136.1, 137.2, 159.6 ppm.

Das Signal bei 159.6 ppm, das von C-4 des Furoxanrings herrührt, weist eine 3,8 Hz-Kopplung zur Methoxygruppe auf, während das Signal bei 110.7 ppm, das von C-3 herrührt, nicht aufgespalten ist. Dies
10 beweist die angegebene Substitution in 4-Position.

Beispiel 25**4-(3-Pyridylmethyloxy)-3-phenylsulfonylfuroxan**

15

Zu einer Lösung von 30 g 3,4-Diphenylsulfonylfuroxan in 360 ml Aceton werden nacheinander 26,7 g 3-Hydroxymethylpyridin gelöst in 100 ml Aceton und 4,9 g Natriumhydroxid gelöst in 40 ml Wasser zugegeben. Nach 30 min wird das ausgefallene Natriumphenylsulfonat abgesaugt, und das Filtrat wird eingengt. Der Rückstand wird durch Chromatographie über Kieselgel (Laufmittel : Essigester) gefolgt von
20 Umkristallisation aus Ethanol gereinigt.

Man erhält 20,2 g (74%) 4-(3-Pyridylmethyloxy)-3-phenylsulfonylfuroxan

Fp.: 121°C

Beispiel 26

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4-(Methoxy-tri(ethylenoxy))-3-phenylsulfonylfuroxan

Analog Beispiel 25 wurden aus 6,0 g 3,4-Diphenylsulfonylfuroxan, 5,8 g Triethylenglykolmonomethylether und 1,0 g Natriumhydroxid 4,3 g (68%) 4-(Methoxy-tri(ethylenoxy))-3-phenylsulfonylfuroxan erhalten,
30 das nicht zur Kristallisation gebracht werden konnte.

Elementaranalyse:					
gefunden:	46,4% C,	5,4% H,	7,1% N,	32,5% O,	9,1% S
berechnet:	46,4% C,	5,2% H,	7,2% N,	33,0% O,	8,3% S

35

Beispiel 27

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4-[2-(N-Benzyl-N-methylamino)-ethyloxy]-3-phenylsulfonylfuroxanhydrochlorid

10,0 g 3,4-Diphenylsulfonylfuroxan, 13,5 g N-Benzyl-N-methylethanolamin und 2,0 g Natriumhydroxid werden analog Beispiel 25 umgesetzt. Das Rohprodukt wird mit CH₂Cl₂/MeOH 99:1 gesäult und anschließend mit etherischer Salzsäure in das Hydrochlorid überführt.

45 Man erhält 2,4 g (20%) 4-[2-(N-Benzyl-N-methylamino)-ethyloxy]-3-phenylsulfonylfuroxanhydrochlorid

Fp.: 171°C

Beispiel 28

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4-[2-(N,N-Dimethylamino)ethyloxy]-3-phenylsulfonylfuroxanhydrochlorid

Die Herstellung erfolgte analog Beispiel 27.

Fp.: 142 - 144°C

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Beispiel 29**4-Methoxycarbonylmethylmercapto-3-phenylsulfonylfuroxan**

- 5 Eine Lösung von 2,0 g (5,5 mmol) 3,4-Diphenylsulfonylfuroxan in 10 ml Aceton wird mit 20 ml Methanol, 0,6 g (5,7 mmol) Thioglykolsäuremethylester und 0,6 g (5,9 mmol) Triethylamin versetzt und 2h unter Stickstoff gerührt. Man gießt die Reaktionsmischung auf 50 ml Wasser, saugt das ausgefallene Produkt ab und reinigt es durch Chromatographie.
- Man erhält 0,75 g (42%) 4-Methoxycarbonylmethylmercapto-3-phenylsulfonylfuroxan.
- 10 Fp.: 118 - 120°C

Beispiel 30**3-Butylmercapto-4-(3-pyridylmethyloxy)-furoxanhydrochlorid**

- 15 Eine Lösung von 5,0 g 4-(3-Pyridylmethyloxy)-3-phenylsulfonylfuroxan (Beispiel 25) und 1,6 g Butylmercaptan in 500 ml Methanol wird mit 3,15 g einer 30-prozentigen Natriummethanolatlösung versetzt und 15 min bei Raumtemperatur gerührt. Die Reaktionsmischung wird vollständig eingeeengt und der Rückstand wird chromatographiert. Das resultierende Öl wird in 100 ml Ether gelöst und durch Zugabe von etherischer
- 20 Salzsäure wird das Hydrochlorid ausgefällt.
- Man erhält 2,3 g (48%) 3-Butylmercapto-4-(3-pyridylmethyloxy)-furoxanhydrochlorid.
- Fp.: 111 - 113°C

Beispiel 31

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4-tert.-Butyl-3-(phenylmercapto)-furoxan

- a) 3,3-Dimethyl-2-oxo-butanthiohydroxamsäure-S-phenylester
- 30 Zu einer Lösung von 12,2 g (89 mmol) Chlorisonitrosopinakolin (Liebigs Ann.Chem. 444 (1925) 113) in 200 ml Ether wird eine Lösung von 9,8 g (89 mmol) Thiophenol in 30 ml Ether und dann eine Lösung von 9,3 g (92 mmol) Triethylamin in 50 ml Ether zugetropft. Nach 2h wird der ausgefallene Niederschlag abgesaugt, das Filtrat wird eingeeengt und durch Verrühren mit Petrolether zur Kristallisation gebracht.
- Man erhält 12 g (56%) 3,3-Dimethyl-2-oxo-butanthiohydroxamsäure-S-phenylester.
- Fp.: 110 - 111°C
- 35 b) 3,3-Dimethyl-2-hydroxyimino-butanthiohydroxamsäure-S-phenylester
- Eine Mischung von 60 g (0,25 mol) 3,3-Dimethyl-2-oxobutanthiohydroxamsäure-S-phenylester, 52,7 g (0,76 mol) Hydroxylammoniumchlorid und 62,2 g (0,76 mol) Natriumacetat in 250 ml Wasser und 250 ml Ethanol wird 18h auf 80°C erhitzt. Man versetzt die Reaktionsmischung mit 1500 ml Wasser, rührt über Nacht und saugt das ausgefallene Produkt ab. Nach Umkristallisation aus Isopropanol erhält man 35 g
- 40 (55%) 3,3-Dimethyl-2-hydroxyimino-butanthiohydroxamsäure-S-phenylester.
- Fp.: 178 - 180°C
- c) Zu einer Suspension von 33,0 g (0,13 mol) 3,3-Dimethyl-2-hydroxyiminobutanthiohydroxamsäure-S-phenylester in 400 ml Ether werden 12,0 g (0,13 mol) Distickstofftetroxid zugetropft. Nach 2h bei Raumtemperatur wird der Ansatz am Rotationsverdampfer eingeeengt, und der Rückstand wird aus
- 45 Isopropanol umkristallisiert.
- Man erhält 24,0 g (73%) 4-tert.-Butyl-3-(phenylmercapto)-furoxan.
- Fp.: 55°C

Beispiel 32

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4-tert.-Butyl-3-phenylsulfinylfuroxan

- Zu einer Lösung von 3,0 g (12 mmol) 4-tert.-Butyl-3-(phenylmercapto)-furoxan in 30 ml Trifluoressigsäure werden 4,7 g (48 mmol) einer 35%igen Wasserstoffperoxidlösung zugetropft. Nach genau 7 min wird
- 55 die Reaktionsmischung auf 90 g Eiswasser gegossen und das ausgefallene Produkt wird abgesaugt. Nach Umkristallisation aus Ethanol/Wasser 3:2 werden 2,9 g (91%) 4-tert.-Butyl-3-phenylsulfinylfuroxan erhalten.
- Fp.: 89 - 91°C

Beispiel 33**4-tert.-Butyl-3-phenylsulfonylfuroxan**

5 Eine Lösung von 14,8 g (59 mmol) 4-tert.-Butyl-3-(phenylmercapto)-furoxan in 140 ml Trifluoressigsäure und 25 g (257 mmol) 35% Wasserstoffperoxid wird 24h bei Raumtemperatur gerührt. Man gießt auf 350 g Eiswasser, saugt den Niederschlag ab, kristallisiert aus Ethanol um und erhält 15,1 g (90%) 4-tert.-Butyl-3-phenylsulfonylfuroxan.
Fp.: 90 - 92°C

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Beispiel 34**4-tert.-Butyl-3-butylmercaptofuroxan**

15 Zu einer Suspension von 10,0 g (35 mmol) 4-tert.-Butyl-3-phenylsulfonylfuroxan in 150 ml Methanol werden nacheinander 3,7 g (41 mmol) Butylmercaptan und 7,4 g (41 mmol) 30%ige Natriummethanolatlösung zugegeben. Man rührt 3h bei Raumtemperatur unter Stickstoff und destilliert dann das Lösungsmittel ab. Der Rückstand wird in 300 ml Cyclohexan und 100 ml Wasser aufgenommen, die wäßrige Phase 1x mit Cyclohexan extrahiert und die vereinigten organischen Phasen werden eingengt. Nach chromatographischer Reinigung erhält man 5,5 g (67%) 4-tert.-Butyl-3-butylmercaptofuroxan.

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Beispiel 35**4-tert.-Butyl-3-butylsulfinylfuroxan**

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Aus 4-tert.-Butyl-3-butylmercaptofuroxan wurde analog Beispiel 32 4-tert.-Butyl-3-butylsulfinylfuroxan als Öl erhalten.

$^{13}\text{C-NMR}$: δ = 163,8 (s), 116,6 (s), 47,9 (t), 33,4 (s), 28,0 (q), 24,2 (t), 21,1 (t), 13,3 (q).

Beispiel 36**4-tert.-Butyl-3-butylsulfonylfuroxan**

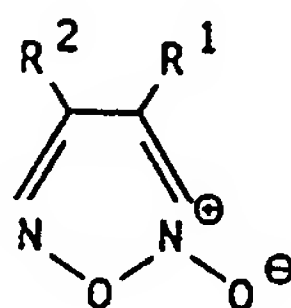
35 Aus 4-tert.-Butyl-3-butylmercaptofuroxan wurde analog Beispiel 33 4-tert.-Butyl-3-butylsulfonylfuroxan erhalten.

Fp.: 77 - 79°C

Patentansprüche

40 1. Furoxane der allgemeinen Formel I

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(I)

50 worin einer der Reste R^1 und R^2 für $-\text{S}(\text{O})_n-\text{R}^3$ und der andere für $(\text{C}_1-\text{C}_{10})$ -Alkyl, (C_3-C_7) -Cycloalkyl, $-\text{CONR}^4\text{R}^5$, $-\text{CN}$ oder $-\text{XR}^6$ steht, wobei

n 0, 1 oder 2 bedeutet;

R^3 $(\text{C}_1-\text{C}_{10})$ -Alkyl, Hydroxy- $(\text{C}_1-\text{C}_{10})$ -alkyl, $\text{R}^7\text{R}^8\text{N}-(\text{C}_1-\text{C}_{10})$ -alkyl, $(\text{C}_2-\text{C}_{22})$ -Alkyl, das durch ein, zwei oder drei Sauerstoffatome unterbrochen ist, (C_3-C_7) -Cycloalkyl, $(\text{C}_7-\text{C}_{10})$ -Aralkyl, $-(\text{CH}_2)_m\text{COY}$, Pyridylmethyl, $(\text{C}_6-\text{C}_{14})$ -Aryl 5- bis 14-gliedriges Heteroaryl, $(\text{C}_6-\text{C}_{14})$ -Aryl oder 5- bis 14-gliedriges Heteroaryl, die ein oder mehrfach substituiert sind durch einen oder mehrere Gruppen aus der Reihe (C_1-C_5) -Alkyl, (C_3-C_7) -Cycloalkyl, Formyl, (C_1-C_4) -Alkylcarbonyl, Amino, (C_1-C_5) -Alkylamino, Di- (C_1-C_5) -alky-

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- lamino, Hydroxy, (C₁-C₅)-Alkoxy, Nitro, Cyano oder Halogen, oder -CH₂CH₂SCOO-(C₁-C₄)-Alkyl bedeutet;
- 5 R⁴ und R⁵ unabhängig voneinander Wasserstoff bedeuten oder wie R³ definiert sind;
 R⁶ unabhängig von diesem wie R³ definiert ist, wobei -CH₂CH₂SCOO(C₁-C₄)-Alkyl ausgeschlossen ist und wobei, falls X für Schwefel steht, R⁶ zusammen mit R³ eine Ethylengruppe bilden kann.
- R⁷ und R⁸ unabhängig voneinander Wasserstoff, (C₁-C₁₀)-Alkyl, (C₇-C₁₀)-Aralkyl oder (C₆-C₁₄)-Aryl, das wie in der Definition von R³ angegeben substituiert sein kann, bedeuten;
- X Sauerstoff oder Schwefel bedeutet;
- 10 Y Hydroxy, (C₁-C₄)-Alkoxy, Amino, (C₁-C₄)-Alkylamino oder Di-(C₁-C₄)-Alkylamino bedeutet; und
- m 1, 2 oder 3 bedeutet;

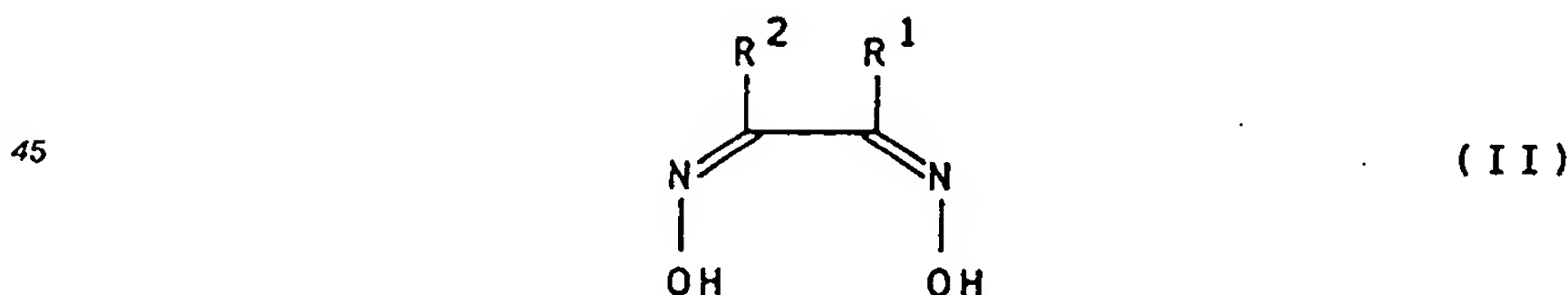
sowie deren pharmakologisch annehmbare Salze, wobei, wenn einer der beiden Reste R¹ und R² für Methyl steht, R³ nicht Phenyl oder durch Methyl, Methoxy, Chlor oder Fluor para-substituiertes Phenyl sein kann; wenn einer der beiden Reste R¹ und R² für Methyl steht und n = 0 oder 2 bedeutet, R³ nicht Methyl oder Ethyl sein kann; wenn einer der beiden Reste R¹ und R² für Methyl steht und n = 2 bedeutet, R³ nicht Benzyl sein kann; und wenn einer der beiden Reste R¹ und R² für Ethoxy steht, der andere nicht -SO₂C₆H₅ oder -SO₂C₆H₄-CH₃ sein kann.

- 20 2. Furoxane gemäß Anspruch 1, dadurch gekennzeichnet, daß der Rest -S(O)_nR³ -S(O)_n-(C₁-C₄)-Alkyl, -S(O)_n-Hydroxy-(C₁-C₄)-alkyl, -S(O)_n-Cyclohexyl, -S(O)_nCH₂COY', worin Y' Hydroxy oder (C₁-C₄)-Alkoxy bedeutet, -S(O)_n-Phenyl oder -S(O)_n-CH₂CH₂SCOO(C₁-C₄)-alkyl bedeutet.
- 25 3. Furoxane gemäß Anspruch 1 und/oder 2, dadurch gekennzeichnet, daß derjenige der Reste R¹ und R², der nicht für -S(O)_nR³ steht, (C₁-C₄)-Alkyl, -CONHR⁴, worin R⁴ Wasserstoff, (C₁-C₄)-Alkyl oder durch Halogen substituiertes Phenyl bedeutet, -CN, Cyclohexylthio, Phenylthio, (C₁-C₄)-Alkoxy, eine Gruppe der Formel



35 worin Z Wasserstoff oder Methyl, x 1, 2 oder 3 und Alk (C₁-C₆)-Alkyl bedeutet, Pyrid-3-yl-methyloxy, R⁷R⁸-N-(C₁-C₄)-alkoxy, worin R⁷ und R⁸ unabhängig voneinander Methyl oder Benzyl bedeuten, oder SCH₂COY', worin Y' wie in Anspruch 2 angegeben, definiert ist, bedeutet.

- 40 4. Verfahren zur Herstellung von Furoxanen der allgemeinen Formel I gemäß einem oder mehreren der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß eine Verbindung der allgemeinen Formel II



50 worin R¹ und R² wie in Anspruch 1 angegeben definiert sind, oxidiert wird.

5. Verwendung von Furoxanen der allgemeinen Formel I gemäß einem der Ansprüche 1 bis 3 zur Bekämpfung und Vorbeugung von Erkrankungen des kardiovaskulären Systems.
- 55 6. Verwendung von Furoxanen der allgemeinen Formel I gemäß einem der Ansprüche 1 bis 3 zur Behandlung erektiler Dysfunktionen.

7. Pharmazeutisches Präparat, dadurch gekennzeichnet, daß es ein Furoxan der allgemeinen Formel I gemäß einem der Ansprüche 1 bis 3, oder ein pharmakologisch annehmbares Salz davon als Wirkstoff zusammen mit pharmazeutisch annehmbaren Träger- und Zusatzstoffen und gegebenenfalls noch ein oder mehrere andere pharmakologische Wirkstoffe enthält.

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EP 95 10 6885

EINSCHLÄGIGE DOKUMENTE			
Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int.Cl.6)
A,D	WO-A-94 01422 (CHIESI FARMACEUTICI SPA) * Tabelle 2, Seiten 10-12; Ansprüche * ---	1,5-7	C07D271/08 A61K31/41 C07D413/12 C07D498/04
A,D	EP-A-0 571 795 (CASSELLA AG) * Seite 4, Zeile 47 - Seite 5, Zeile 7; Ansprüche * ---	1,4-7	
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			RECHERCHIERTE SACHGEBIETE (Int.Cl.6)
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<p>Nach Auffassung der Recherchenabteilung entspricht die vorliegende europäische Patentanmeldung den Vorschriften des Europäischen Patentübereinkommens so wenig, daß es nicht möglich ist, auf der Grundlage einiger Patentansprüche sinnvolle Ermittlungen über den Stand der Technik durchzuführen.</p> <p>Vollständig recherchierte Patentansprüche: Unvollständig recherchierte Patentansprüche: Nicht recherchierte Patentansprüche: Grund für die Beschränkung der Recherche:</p> <p>Siehe Ergänzungsblatt C</p>			
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A	CHEMICAL ABSTRACTS, vol. 105, no. 13, 1986 Columbus, Ohio, US; abstract no. 114403a, * Zusammenfassung * & DATABASE REGISTRY CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US STN, *RN: 104151-75-9, 104151-74-8; 104151-88-4; 104151-87-3 * & KHIM. GETEROSIKL. SOEDIN, Nr. 2, 1986 Seiten 264-266, V.G. ANDRIANOV ET AL ---	1	
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			RECHERCHIERTE SACHGEBIETE (Int.Cl.6)



EP 95 10 6885

-C-

Bemerkung: Obwohl die Ansprüche 5,6
sich auf ein Verfahren zur Behandlung des
menschlichen/tierischen Körpers
(Diagnostizierverfahren, das am menschlichen/
tierischen Körper vorgenommen wird,)
beziehen (Art. 52(4)EPU), wurde die
Recherche durchgeführt und gründete sich auf
die angeführten Wirkungen der Verbindung/
Zusammensetzung.

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<p>(51) International Patent Classification ⁷ : A61K 31/341, 31/4164, 31/417, 31/427, 31/4453, C07D 211/06, 233/64, 277/28, 277/48, 277/52, 307/52</p>	<p>A1</p>	<p>(11) International Publication Number: WO 00/28988 (43) International Publication Date: 25 May 2000 (25.05.00)</p>
<p>(21) International Application Number: PCT/US99/27207 (22) International Filing Date: 17 November 1999 (17.11.99) (30) Priority Data: 60/108,877 17 November 1998 (17.11.98) US 60/140,839 28 June 1999 (28.06.99) US (71) Applicant (for all designated States except US): NITROMED, INC. [US/US]; 12 Oak Park Drive, Bedford, MA 01730 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): GARVEY, David, S. [US/US]; 10 Grand Hill Drive, Dover, MA 02030 (US). LETTIS, L., Gordon [AU/US]; 12 Abbott Road, Dover, MA 02030 (US). WANG, Tiansheng [CN/US]; 2 Dumbur Way, Concord, MA 01742 (US). (74) Agents: GRIEFF, Edward, D. et al.; Hale and Dorr LLP, Suite 1000, 1455 Pennsylvania Avenue, N.W., Washington, DC 20004 (US).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: NITROSATED AND NITROSYLATED H₂ RECEPTOR ANTAGONIST COMPOUNDS, COMPOSITIONS AND METHODS OF USE</p> <p>(57) Abstract</p> <p>The present invention describes novel nitrosated and/or nitrosylated H₂ receptor antagonist compounds, and novel compositions comprising at least one H₂ receptor antagonist compound that is optionally substituted with at least one NO and/or NO₂ group, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase. The present invention also describes methods for treating and/or preventing gastrointestinal disorders; improving gastroprotective properties of H₂ receptor antagonists; decreasing the recurrence of ulcers; facilitating ulcer healing; preventing and/or treating inflammations and microbial infections, ophthalmic diseases and disorders, multiple sclerosis, and viral infections; and decreasing or reducing the gastrointestinal toxicity associated with the use of nonsteroidal antiinflammatory compounds.</p>		

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**NITROSATED AND NITROSYLATED H₂ RECEPTOR ANTAGONIST
COMPOUNDS, COMPOSITIONS AND METHODS OF USE
RELATED APPLICATIONS**

This application claims priority to U.S. Provisional Application No.
5 60/108,877 filed November 17, 1998 and U.S. Provisional Application No.
60/140,839 filed June 28, 1999.

FIELD OF THE INVENTION

The present invention describes novel nitrosated and/or nitrosylated H₂
receptor antagonist compounds, and novel compositions comprising at least one H₂
10 receptor antagonist compound that is optionally substituted with at least one NO
and/or NO₂ group, and, optionally, at least one compound that donates, transfers
or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates
endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric
oxide synthase. The present invention also provides methods for treating and/or
15 preventing gastrointestinal disorders; improving gastroprotective properties of H₂
receptor antagonists; decreasing the recurrence of ulcers; facilitating ulcer healing;
treating and/or preventing inflammations and microbial infections, ophthalmic
diseases and disorders, multiple sclerosis, and viral infections; and decreasing or
reducing the gastrointestinal toxicity associated with the use of nonsteroidal
20 antiinflammatory compounds.

BACKGROUND OF THE INVENTION

H₂ receptor antagonists are a well known class of drugs used in the
management of gastrointestinal disorders. H₂ antagonists competitively inhibit the
interaction of histamine with H₂ receptors. Although H₂ receptors are present in
25 numerous tissues, including vascular and bronchial smooth muscle, they appear to
have a minimal role in modulating physiological functions other than gastric
secretion.

H₂ receptor antagonists inhibit gastric acid secretion elicited by histamine
and other H₂ receptor agonists in a dose-dependent, competitive manner. The H₂
30 receptor antagonists also inhibit acid secretion elicited by gastrin and, to a lesser
extent, by muscarinic agonists. H₂ receptor antagonists inhibit basal (fasting) and
nocturnal acid secretion and that stimulated by food, sham feeding, fundic
distention, and various pharmacological agents. The H₂ receptor antagonists

reduce both the volume of gastric juice secreted and its hydrogen ion (H^+) concentration. Despite their good antisecretory properties, H_2 receptor antagonists are not unanimously recognized as gastroprotective agents. In addition, there is a high relapse rate associated with treating gastrointestinal disorders with H_2 receptor antagonists as they do not eliminate *Helicobacter pylori* (*Campylobacter pylori*), the bacteria responsible for peptic ulcer disease, gastric lymphoma and adenocarcinoma.

A variety of adverse reactions have been ascribed to H_2 receptor antagonists, such as cimetidine and ranitidine, reflecting, in part, the very large number of patients who have been treated with these drugs. The incidence of adverse reactions is low, and the adverse reactions are generally minor. The low incidence is attributable in part to the limited function of H_2 receptors in organs other than the stomach and to the poor penetration of these agents across the blood-brain barrier.

The most common side effects of H_2 receptor antagonists, such as cimetidine, are headache, dizziness, nausea, myalgia, skin rashes, and itching. The incidence of symptoms related to the central nervous system (CNS) appears to be higher in the elderly and in patients with impaired renal function. Loss of libido, impotence and gynecomastia are sometimes observed in patients who receive long-term therapy with high doses of H_2 receptor antagonists, such as cimetidine.

Sorba et al, *Arzneim-Forsch Drug Res.*, 47(II):849-854 (1997), the disclosure of which is incorporated by reference herein in its entirety, have developed a drug that combines a H_2 receptor antagonist with a nitric oxide (NO)-donor furoxan moiety. This drug is reported to retain weaker H_2 receptor antagonist activity relative to the parent drug but shows a NO-dependent gastroprotective effect.

U.S. Patent No. 5,403,830, the disclosure of which is incorporated by reference herein in its entirety, describes pharmaceutical compositions and methods of treating gastrointestinal disorders by administering bismuth-containing agents in conjunction with a H_2 receptor antagonist. U.S. Patent Nos. 5,403,830, and 5,407,688, and Ivnov et al, *J. Pharm. Pharmacol.*, 48:297-301 (1996) and Marazova et al, *J. Pharm. Pharmacol.*, 49:791-795 (1997), the disclosures of each of which are incorporated by reference herein in their entirety, describe treating or preventing gastrointestinal disorders by administering bismuth containing agents. U.S. Patent Nos. 4,705,683, 4,900,741, 5,112,850 and 5,656,652, the disclosures of which are

incorporated by reference herein in their entirety, describe administering H₂ receptor antagonists with polyacrylates, antimuscarinic agents, trapencine and antacids, respectively. U.S. Patent No. 5,656,652, the disclosure of which is incorporated by reference herein in its entirety, describes the use of H₂ antagonists and antacids for the treatment of gastrointestinal disorders.

5 The administration of NSAIDs, such as indomethacin or ibuprofen, with H₂ receptor antagonists, such as cimetidine, is described in U.S. Patent Nos. 5,037,815 and 4,279,906 and in WO 94/07541, the disclosure of each of which is incorporated by reference herein in its entirety. U.S. Patent Nos. 5,102,902, 5,541,212 and 10 5,578,597, the disclosures of each of which are incorporated by reference herein in their entirety, disclose the use of H₂ receptor antagonists for treating multiple sclerosis and retrovirus infections.

There is a need in the art for H₂ receptor antagonist compounds that have gastroprotective properties, decrease the recurrence of ulcers, facilitate ulcer healing and that can be used at low dosages. The present invention is directed to these, as well as other, important ends.

SUMMARY OF THE INVENTION

The present invention provides compounds comprising a H₂ receptor antagonist to which is linked at least one NO and/or NO₂ group (i.e., nitrosylated and/or nitrosated). The H₂ receptor antagonists can be, for example, histamine 20 analogs that contain a bulky side chain instead of an ethylamine moiety and retain the imidazole ring of histidine, such as cimetidine. The imidazole ring can be replaced by a furan (e.g., rantidine) or a thiazole (e.g., famotidine, nizatidine). The H₂ receptor antagonists can also be, for example, amide derivatives, such as, for example, roxatidine or a guanidino derivative, such as, for example, ebrotidine or 25 famotidine. The present invention also provides compositions comprising such compounds in a pharmaceutically acceptable carrier.

Another aspect of the invention provides compositions comprising at least one H₂ receptor antagonist, that is optionally substituted with at least one NO and/or NO₂ group (i.e., nitrosylated and/or nitrosated), and at least one compound 30 that donates, transfers or releases nitric oxide and/or stimulates endogenous production of nitric oxide (NO) or endothelium-derived relaxing factor (EDRF) *in vivo* and/or is a substrate for nitric oxide synthase.

Yet another aspect of the present invention provides methods for treating gastrointestinal disorders, improving the gastroprotective properties of H_2 receptor antagonists, increasing the rate of ulcer healing, decreasing the rate of recurrence of ulcers, treating inflammations, treating ophthalmic diseases and disorders, and
5 treating microbial infections in a patient in need thereof which comprises administering to the patient at least one H_2 receptor antagonist compound, that is optionally substituted with at least one NO and/or NO_2 group (i.e., nitrosylated and/or nitrosated), and, optionally, at least one compound that donates, transfers or releases nitric oxide and/or stimulates endogenous production of NO or EDRF
10 *in vivo* and/or is a substrate for nitric oxide synthase. The H_2 receptor antagonist that is optionally linked to at least one NO and/or NO_2 group and nitric oxide donor can be administered separately or as components of the same composition.

The present inventions also describes methods to decrease or reverse gastrointestinal toxicity and facilitate ulcer healing resulting from the
15 administration of nonsteroidal antiinflammatory drugs (NSAIDs); methods to improve the gastroprotective properties, anti-*Helicobacter* properties and antacid properties of H_2 receptor antagonists; methods for preventing or treating gastrointestinal disorders; methods for treating multiple sclerosis; methods for treating ophthalmic diseases and disorders; and methods for treating viral
20 infections, such as HIV disease. The nitrosated and/or nitrosylated NSAID and nitric oxide donor can be administered separately or as components of the same composition. These and other aspects of the present invention are explained in detail herein.

BRIEF DESCRIPTION OF THE FIGURES

25 Fig. 1 is the synthetic scheme for the preparation of nitrite-containing guanidino derivatives of the compound of formula (I).

Fig. 2 is the synthetic scheme for the preparation of a nitrosothiol-containing guanidino derivatives of the compound of formula (II).

30 Fig. 3 is the synthetic scheme for the preparation of nitrite derivatives of the compound of formula (II).

Fig. 4 is the synthetic scheme for the preparation of nitrosothiol derivatives of the compound of formula (II).

Fig. 5 is the synthetic scheme for the preparation of nitrite-containing

guanidino derivatives of the compound of formula (III).

Fig. 6 is the synthetic scheme for the preparation of nitrosothiol-containing guanidino derivatives of the compound of formula (III).

Fig. 7 shows the gastric lesion scores of (a) vehicle alone (open bar, n=14); (b) cimetidine in vehicle (stipped bar); and (c) example 1 (nitrosylated cimetidine) in vehicle (checked bar). Cimetidine at 160 $\mu\text{mol/kg}$ (n=6) and 320 $\mu\text{mol/kg}$ (n=16) did not significantly inhibit the formation of gastric lesions relative to vehicle alone. Example 1 (nitrosylated cimetidine) at 160 $\mu\text{mol/kg}$ (n=9) and 320 $\mu\text{mol/kg}$ (n=18) inhibited the formation of gastric lesions relative to vehicle alone ($p<0.05$). At the higher concentration, the gastric lesion score of example 1 and cimetidine were significantly different ($p<0.05$).

DETAILED DESCRIPTION OF THE INVENTION

As used throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

"Gastrointestinal disorder" refers to any disease or disorder of the upper gastrointestinal tract of a patient including, for example, peptic ulcers, stress ulcers, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, short-bowel (anastomosis) syndrome, hypersecretory states associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia, and bleeding peptic ulcers that result, for example, from neurosurgery, head injury, severe body trauma or burns.

"Upper gastrointestinal tract" refers to the esophagus, the stomach, the duodenum and the jejunum.

"Ulcers" refers to lesions of the upper gastrointestinal tract lining that are characterized by loss of tissue. Such ulcers include gastric ulcers, duodenal ulcers and gastritis.

"H₂ receptor antagonist" refers to any compound that reversibly or irreversibly blocks the activation of any H₂ receptor.

"NSAID" refers to a nonsteroidal anti-inflammatory compound or a nonsteroidal anti-inflammatory drug. NSAIDs inhibit cyclooxygenase, the enzyme responsible for the biosyntheses of the prostaglandins and certain autocoid inhibitors, including inhibitors of the various isozymes of cyclooxygenase (including but not limited to cyclooxygenase-1 and -2), and as inhibitors of both

cyclooxygenase and lipoxygenase.

"Patient" refers to animals, preferably mammals, more preferably humans.

"Transdermal" refers to the delivery of a compound by passage through the skin and into the blood stream.

5 "Transmucosal" refers to delivery of a compound by passage of the compound through the mucosal tissue and into the blood stream.

"Penetration enhancement" or "permeation enhancement" refers to an increase in the permeability of the skin or mucosal tissue to a selected pharmacologically active compound such that the rate at which the compound permeates through the skin or mucosal tissue is increased.

10 "Carriers" or "vehicles" refers to carrier materials suitable for compound administration and include any such material known in the art such as, for example, any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is non-toxic and which does not interact with any components of the composition in a deleterious manner.

"Nitric oxide adduct" or "NO adduct" refers to compounds and functional groups which, under physiological conditions, can donate, release and/or directly or indirectly transfer any of the three redox forms of nitrogen monoxide (NO^+ , NO^- , NO^\bullet), such that the biological activity of the nitrogen monoxide species is expressed at the intended site of action.

20 "Nitric oxide releasing" or "nitric oxide donating" refers to methods of donating, releasing and/or directly or indirectly transferring any of the three redox forms of nitrogen monoxide (NO^+ , NO^- , NO^\bullet), such that the biological activity of the nitrogen monoxide species is expressed at the intended site of action.

25 "Nitric oxide donor" or "NO donor" refers to compounds that donate, release and/or directly or indirectly transfer a nitrogen monoxide species, and/or stimulate the endogenous production of nitric oxide or endothelium-derived relaxing factor (EDRF) *in vivo* and/or elevate endogenous levels of nitric oxide or EDRF *in vivo*. "NO donor" also includes compounds that are substrates for nitric oxide synthase.

30 "Alkyl" refers to a lower alkyl group, a haloalkyl group, an alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, as defined herein.

"Lower alkyl" refers to branched or straight chain acyclic alkyl group comprising one to about ten carbon atoms (preferably one to about eight carbon atoms, more preferably one to about six carbon atoms). Exemplary lower alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, neopentyl, iso-amyl, hexyl, octyl, and the like.

"Haloalkyl" refers to a lower alkyl group, an alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, as defined herein, to which is appended one or more halogens, as defined herein. Exemplary haloalkyl groups include trifluoromethyl, chloromethyl, 2-bromobutyl, 1-bromo-2-chloro-pentyl, and the like.

"Alkenyl" refers to a branched or straight chain C_2 - C_{10} hydrocarbon (preferably a C_2 - C_8 hydrocarbon, more preferably a C_2 - C_6 hydrocarbon) which can comprise one or more carbon-carbon double bonds. Exemplary alkenyl groups include propylenyl, buten-1-yl, isobutenyl, penten-1-yl, 2,2-methylbuten-1-yl, 3-methylbuten-1-yl, hexan-1-yl, hepten-1-yl, octen-1-yl, and the like.

"Alkynyl" refers to an unsaturated acyclic C_2 - C_{10} hydrocarbon (preferably a C_2 - C_8 hydrocarbon, more preferably a C_2 - C_6 hydrocarbon) which can comprise one or more carbon-carbon triple bonds. Exemplary alkynyl groups include ethynyl, propynyl, butyn-1-yl, butyn-2-yl, pentyl-1-yl, pentyl-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyl-2-yl, hexyl-3-yl, 3,3-dimethyl-butyn-1-yl, and the like.

"Bridged cycloalkyl" refers to two or more cycloalkyl groups, heterocyclic groups, or a combination thereof fused via adjacent or non-adjacent atoms. Bridged cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, carboxyl, alkylcarboxylic acid, aryl, amidyl, ester, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo and nitro. Exemplary bridged cycloalkyl groups include adamantyl, decahydronaphthyl, quinuclidyl, 2,6-dioxabicyclo[3.3.0]octane, 7-oxabicyclo[2.2.1]heptyl, 8-azabicyclo[3.2.1]oct-2-enyl and the like.

"Cycloalkyl" refers to a saturated or unsaturated cyclic hydrocarbon comprising from about 3 to about 8 carbon atoms. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, arylamino,

diarylamino, alkylarylamino, aryl, amidyl, ester, hydroxy, halo, carboxyl, alkylcarboxylic acid, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo and nitro. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cyclohepta,1,3-dienyl, and the like.

5 "Heterocyclic ring or group" refers to a saturated or unsaturated cyclic hydrocarbon group having about 2 to about 10 carbon atoms (preferably about 4 to about 6 carbon atoms) where 1 to about 4 carbon atoms are replaced by one or more nitrogen, oxygen and/or sulfur atoms. Sulfur may be in the thio, sulfinyl or sulfonyl oxidation state. The heterocyclic ring or group can be fused to an aromatic
10 hydrocarbon group. Heterocyclic groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, hydroxy, oxo, thial, halo, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, arylcarboxylic ester, amidyl, ester, carboxamido,
15 alkylcarboxamido, arylcarboxamido, sulfonic acid, sulfonic ester, sulfonamido and nitro. Exemplary heterocyclic groups include pyrrolyl, 3-pyrrolinyl, 4,5,6-trihydro-2H-pyranyl, pyridinyl, 1,4-dihydropyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrahydrofuranyl, tetrazolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolindinyl, oxazolindinyl,
20 1,3-dioxolanyl, 2-imidazonlinyl, imidazolindinyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazolyl, quinolinyl, and the like.

25 "Heterocyclic compounds" refer to mono- and polycyclic compounds comprising at least one aryl or heterocyclic ring.

"Aryl" refers to a monocyclic, bicyclic, carbocyclic or heterocyclic ring system comprising one or two aromatic rings. Exemplary aryl groups include phenyl, pyridyl, naphthyl, quinoyl, tetrahydronaphthyl, furanyl, indanyl, indenyl, indoyl,
30 and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, hydroxy, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl,

arylcarboxylic acid, arylcarboxylic ester, alkylcarbonyl, arylcarbonyl, amidyl, ester, carboxamido, alkylcarboxamido, carbomyl, sulfonic acid, sulfonic ester, sulfonamido and nitro. Exemplary substituted aryl groups include tetrafluorophenyl, pentafluorophenyl, sulfonamide, alkylsulfonyl, arylsulfonyl, and the like.

"Alkylaryl" refers to an alkyl group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary alkylaryl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl, and the like.

"Arylalkyl" refers to an aryl radical, as defined herein, attached to an alkyl radical, as defined herein.

"Cycloalkylalkyl" refers to a cycloalkyl radical, as defined herein, attached to an alkyl radical, as defined herein.

"Heterocyclicalkyl" refers to a heterocyclic ring radical, as defined herein, attached to an alkyl radical, as defined herein.

"Arylheterocyclic ring" refers to a bi- or tricyclic ring comprised of an aryl ring, as defined herein, appended via two adjacent carbon atoms of the aryl ring to a heterocyclic ring, as defined herein. Exemplary arylheterocyclic rings include dihydroindole, 1,2,3,4-tetra-hydroquinoline, and the like.

"Alkoxy" refers to $R_{50}O-$, wherein R_{50} is an alkyl group, as defined herein. Exemplary alkoxy groups include methoxy, ethoxy, t-butoxy, cyclopentyloxy, and the like.

"Arylalkoxy or alkoxyaryl" refers to an alkoxy group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary arylalkoxy groups include benzyloxy, phenylethoxy, chlorophenylethoxy, and the like.

"Alkoxyalkyl" refers to an alkoxy group, as defined herein, appended to an alkyl group, as defined herein. Exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, isopropoxymethyl, and the like.

"Alkoxyhaloalkyl" refers to an alkoxy group, as defined herein, appended to a haloalkyl group, as defined herein. Exemplary alkoxyhaloalkyl groups include 4-methoxy-2-chlorobutyl and the like.

"Cycloalkoxy" refers to $R_{54}O-$, wherein R_{54} is a cycloalkyl group or a bridged cycloalkyl group, as defined herein. Exemplary cycloalkoxy groups include cyclopropyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

"Haloalkoxy" refers to a haloalkyl group, as defined herein, to which is appended an alkoxy group, as defined herein. Exemplary haloalkyl groups include 1,1,1-trichloroethoxy, 2-bromobutoxy, and the like.

"Hydroxy" refers to -OH.

5 "Oxo " refers to =O.

"Oxy " refers to $-O^-R_7^+$ wherein R_7 is an organic or inorganic cation.

"Organic cation" refers to a positively charged organic ion. Exemplary organic cations include alkyl substituted ammonium cations, and the like.

10 "Inorganic cation" refers to a positively charged metal ion. Exemplary inorganic cations include Group I metal cations such as for example, sodium, potassium, and the like.

"Hydroxyalkyl" refers to a hydroxy group, as defined herein, appended to an alkyl group, as defined herein.

"Amino" refers to -NH₂.

15 "Nitrate" refers to -O-NO₂.

"Nitrite" refers to -O-NO.

"Thionitrate" refers to -S-NO₂.

"Thionitrite" and "nitrosothiol" refer to -S-NO.

20 "Nitro" refers to the group -NO₂ and "nitrosated" refers to compounds that have been substituted therewith.

"Nitroso" refers to the group -NO and "nitrosylated" refers to compounds that have been substituted therewith.

"Nitrile" and "cyano" refer to -CN.

25 "Halogen" or "halo" refers to iodine (I), bromine (Br), chlorine (Cl), and/or fluorine (F).

"Alkylamino" refers to R₅₀NH-, wherein R₅₀ is an alkyl group, as defined herein. Exemplary alkylamino groups include methylamino, ethylamino, butylamino, cyclohexylamino, and the like.

"Arylamino" refers to R₅₅NH-, wherein R₅₅ is an aryl group, as defined herein.

30 "Dialkylamino" refers to R₅₂R₅₃N-, wherein R₅₂ and R₅₃ are each independently an alkyl group, as defined herein. Exemplary dialkylamino groups include dimethylamino, diethylamino, methyl propargylamino, and the like.

"Diarylamino" refers to R₅₅R₆₀N-, wherein R₅₅ and R₆₀ are each independently

an aryl group, as defined herein.

"Alkylarylamino" refers to $R_{52}R_{55}N-$, wherein R_{52} is an alkyl group, as defined herein, and R_{55} is an aryl group, as defined herein.

5 "Aminoalkyl" refers to an amino group, an alkylamino group, a dialkylamino group, an arylamino group, a diarylamino group, an alkylarylamino group or a heterocyclic ring, as defined herein, to which is appended an alkyl group, as defined herein.

10 "Aminoaryl" refers to an amino group, an alkylamino group, a dialkylamino group, an arylamino group, a diarylamino group, an alkylarylamino group or a heterocyclic ring, as defined herein, to which is appended an aryl group, as defined herein.

"Thio" refers to $-S-$.

"Sulfinyl" refers to $-S(O)-$.

"Methanthial" refers to $-C(S)-$.

15 "Thial" refers to $=S$.

"Sulfonyl" refers to $-S(O)_2-$.

"Sulfonic acid" refers to $-S(O)_2OR_{76}$, wherein R_{76} is a hydrogen, an organic cation or an inorganic cation.

20 "Alkylsulfonic acid" refers to a sulfonic acid group, as defined herein, appended to an alkyl group, as defined herein.

"Arylsulfonic acid" refers to a sulfonic acid group, as defined herein, appended to an aryl group, as defined herein.

"Sulfonic ester" refers to $-S(O)_2OR_{58}$, wherein R_{58} is an alkyl group, an aryl group, an alkylaryl group or an aryl heterocyclic ring, as defined herein.

25 "Sulfonamido" refers to $-S(O)_2N(R_{51})(R_{57})$, wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group, an alkylaryl group, or an arylheterocyclic ring, as defined herein, and R_{51} and R_{57} when taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

30 "Alkylsulfonamido" refers to a sulfonamido group, as defined herein, appended to an alkyl group, as defined herein.

"Arylsulfonamido" refers to a sulfonamido group, as defined herein, appended to an aryl group, as defined herein.

"Alkylthio" refers to $R_{50}S-$, wherein R_{50} is an alkyl group, as defined herein.

"Arylthio" refers to $R_{55}S-$, wherein R_{55} is an aryl group, as defined herein.

"Alkylsulfinyl" refers to $R_{50}-S(O)-$, wherein R_{50} is an alkyl group, as defined herein.

5 "Alkylsulfonyl" refers to $R_{50}-S(O)_2-$, wherein R_{50} is an alkyl group, as defined herein.

"Arylsulfinyl" refers to $R_{55}-S(O)-$, wherein R_{55} is an aryl group, as defined herein.

10 "Arylsulfonyl" refers to $R_{55}-S(O)_2-$, wherein R_{55} is an aryl group, as defined herein.

"Amidyl" refers to $R_{51}C(O)N(R_{57})-$ wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group, an alkylaryl group, or an arylheterocyclic ring, as defined herein.

15 "Ester" refers to $R_{51}C(O)O-$ wherein R_{51} is a hydrogen atom, an alkyl group, an aryl group, an alkylaryl group, or an arylheterocyclic ring, as defined herein.

"Carbamoyl" refers to $-O-C(O)N(R_{51})(R_{57})$, wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group, an alkylaryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined
20 herein.

"Carboxyl" refers to $-C(O)OR_{76}$, wherein R_{76} is a hydrogen, an organic cation or an inorganic cation, as defined herein.

"Carbonyl" refers to $-C(O)-$.

25 "Alkylcarbonyl" refers to $R_{52}-C(O)-$, wherein R_{52} is an alkyl group, as defined herein.

"Arylcarbonyl" refers to $R_{55}-C(O)-$, wherein R_{55} is an aryl group, as defined herein.

"Carboxylic ester" refers to $-C(O)OR_{58}$, wherein R_{58} is an alkyl group, an aryl group, an alkylaryl group or an aryl heterocyclic ring, as defined herein.

30 "Alkylcarboxylic acid" and "alkylcarboxyl" refer to an alkyl group, as defined herein, appended to a carboxyl group, as defined herein.

"Alkylcarboxylic ester" refers to an alkyl group, as defined herein, appended to a carboxylic ester group, as defined herein.

"Arylcarboxylic acid" refers to an aryl group, as defined herein, appended to a carboxyl group, as defined herein.

"Arylcarboxylic ester" and "arylcarboxyl" refer to an aryl group, as defined herein, appended to a carboxylic ester group, as defined herein.

5 "Carboxamido" refers to $-C(O)N(R_{51})(R_{57})$, wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group, an alkylaryl group or an arylheterocyclic ring, as defined herein, and R_{51} and R_{57} when taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

10 "Alkylcarboxamido" refers to an alkyl group, as defined herein, appended to a carboxamido group, as defined herein.

"Arylcarboxamido" refers to an aryl group, as defined herein, appended to a carboxamido group, as defined herein.

15 "Urea" refers to $-N(R_{58})-C(O)N(R_{51})(R_{57})$ wherein R_{51} , R_{57} , and R_{58} are each independently a hydrogen atom, an alkyl group, an aryl group, an alkylaryl group, or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

20 Compounds that donate, transfer or release nitric oxide species *in vivo* have been recognized as having a wide spectrum of advantages and applications. The present invention is based on the unexpected discovery of the effects of such compounds alone and together with one or more H_2 receptor antagonists and/or one or more H_2 receptor antagonists directly or indirectly linked with one or more nitric oxide moieties. Treatment or prevention of gastrointestinal disorders, improved gastroprotective properties, decreased rate of recurrence of ulcers
25 (preferably peptic ulcers), faster ulcer healing, treatment of inflammations, treatment of ophthalmic diseases and disorders and treatment of microbial infections can be obtained by the use of the nitrosated and/or nitrosylated H_2 receptor antagonists of the present invention; or by the use of the nitrosated and/or nitrosylated H_2 receptor antagonists in conjunction with one or more compounds
30 that donate, release or transfer nitric oxide and/or stimulate endogenous production of NO and/or EDRF *in vivo* and/or is a substrate for nitric oxide synthase.

The present invention is also based on the discovery that it is possible to administer at least one H_2 receptor antagonist, optionally linked to at least one NO and/or NO_2 group, and at least one nitric oxide donor to treat gastrointestinal disorders, improve gastroprotective properties, decrease the rate of recurrence of peptic ulcers and increase the rate of ulcer healing of H_2 receptor antagonists, to
5 treat inflammations and microbial infections, and to treat ophthalmic diseases and disorders. H_2 receptor antagonists are compounds that competitively inhibit the interaction of histamine with H_2 receptors. A nitric oxide donor is a compound that contains a nitric oxide moiety and releases or chemically transfers nitric oxide to
10 another molecule, as defined herein.

The compounds and compositions of the present invention are novel and can be used to treat numerous gastrointestinal disorders, inflammations, microbial infections and ophthalmic diseases and disorders. Such gastrointestinal disorders include, for example, peptic ulcers, stress ulcers, gastric hyperacidity, dyspepsia,
15 gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, short-bowel (anastomosis) syndrome, hypersecretory states associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia, and bleeding peptic ulcers that result, for example, from neurosurgery, head injury, severe body trauma or burns. Such inflammations and/or microbial infections include, for example,
20 inflammations and/or infections of the eyes, ears, nose, and/or skin. Such ophthalmic diseases and disorders include, for example, glaucoma, inflammation of the eye and elevation of intraocular pressure. The compounds and compositions of the present invention can also be used as a pre-anesthetic medication in emergency operations to reduce the danger of aspiration of acidic gastric contents

25 The H_2 receptor antagonist compounds that are nitrosated and/or nitrosylated in accordance with the invention and/or are included in the compositions of the invention can be any of those known in the art, including those exemplified below.

Cimetidine (marketed under the trade name TAGAMET® by SmithKline
30 Beecham Pharmaceuticals, Philadelphia, PA) is one of the most widely used anti-secretory agents in the treatment of gastric ulcers. This compound blocks the histamine receptors within the stomach mucosa, thereby preventing histamine molecules from signalling the stomach cells to secrete acid. H_2 receptor blocking

agents that are more potent than cimetidine (e.g. ranitidine, nizatidine) are also widely used. Although the H₂ receptor blocking anti-secretory agents are effective in treating gastrointestinal disorders, they do not have any gastroprotective properties and, in addition, there is a high recurrence of ulcers associated with their use.

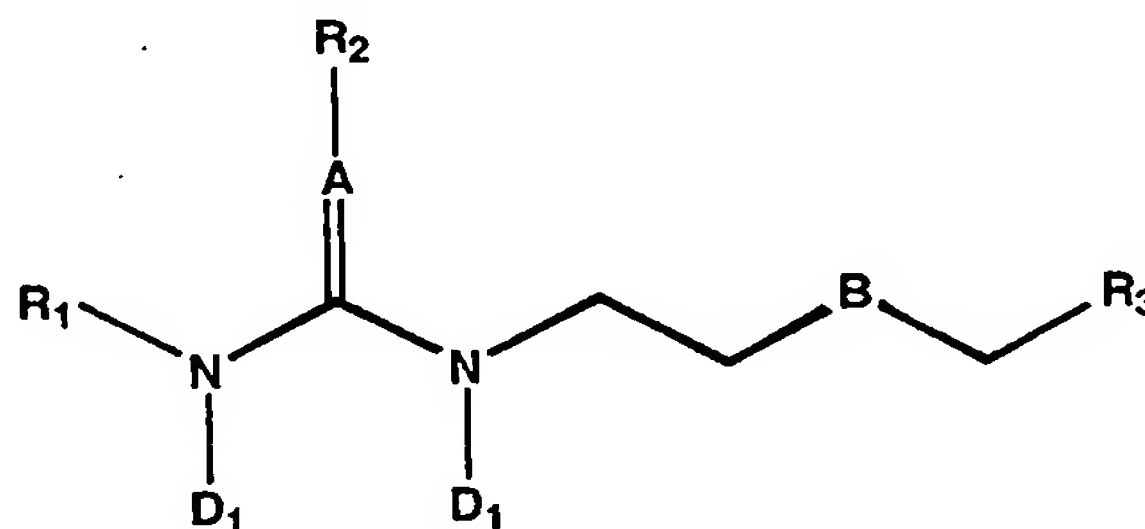
Another group of H₂ receptor antagonists are amide derivatives, which include, for example, roxatidine.

Yet another group of H₂ receptor antagonists are guanidino derivatives, which include, for example, famotidine and ebrotidine.

Other H₂ receptor antagonists contemplated by the present invention include burimamide, metiamide, tiotidine and oxmetidine.

Each of the above contemplated H₂ receptor antagonists is described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, Pgs. 901-915; the Merck Index on CD-ROM, Twelfth Edition, Version 12:1, 1996.

In one embodiment, the present invention describes nitrosated and/or nitrosylated compounds of Formula (I):



(I)

wherein

A is CH, nitrogen or sulfur;

B is oxygen, S(O)_o or CH₂;

o is an integer from 0 to 2;

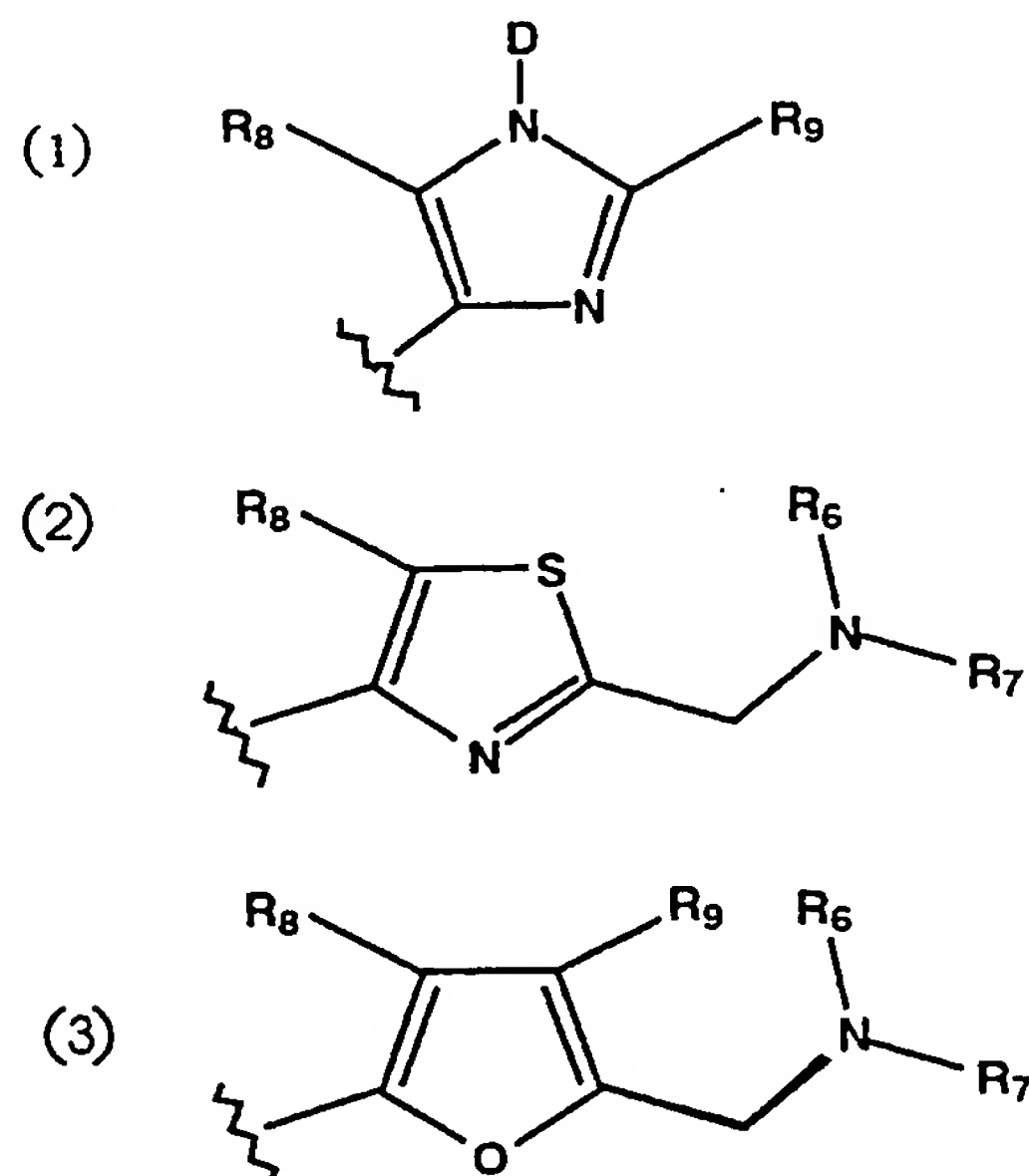
D₁ is a hydrogen atom or D;

R₁ is a hydrogen atom, a lower alkyl group, a cycloalkylalkyl group, a hydroxyalkyl group, an alkoxyalkyl group or an aminoalkyl group;

R₂ is a lone pair of electrons, a nitrile group, a nitro group, an alkylsulfonyl

group, an arylsulfonyl group, an alkylcarbonyl group, a carboxamido group, a carboxylic ester or a cycloalkylalkyl group;

R_3 is:



5 with the proviso that at least one D_i must be D if there is no D designated in the structure;

R_6 and R_7 are each independently K, a hydrogen atom, a lower alkyl group, an alkylaryl group, an arylcarbonyl group, an alkylcarbonyl group, or R_6 and R_7 taken together are a heterocyclic ring;

10 R_8 and R_9 are independently a hydrogen atom or a lower alkyl group;

D is Q or K;

Q is -NO or -NO₂;

K is $-W_a-E_b-(C(R_e)(R_f))_p-E_c-(C(R_e)(R_f))_x-W_d-(C(R_e)(R_f))_y-W_i-E_j-W_g-(C(R_e)(R_f))_z-T-Q$;

a, b, c, d, g, i and j are each independently an integer from 0 to 3;

15 p, x, y and z are each independently an integer from 0 to 10;

W at each occurrence is independently -C(O)-, -C(S)-, -T-, $-(C(R_e)(R_f))_h$ -, an alkyl group, an aryl group, a heterocyclic ring, an arylheterocyclic ring, or $-(CH_2CH_2O)_q$;

20 E at each occurrence is independently -T-, an alkyl group, an aryl group, $-(C(R_e)(R_f))_h$ -, a heterocyclic ring, an arylheterocyclic ring, or $-(CH_2CH_2O)_q$;

h is an integer from 1 to 10;

q is an integer of from 1 to 5;

R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylaryl amino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an alkoxy, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkyl carboxamido, an aryl carboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a carbamoyl, a urea, a nitro, -T-Q, or $(C(R_e)(R_f))_k$ -T-Q, or R_e and R_f taken together are a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group;

k is an integer from 1 to 3;

T at each occurrence is independently a covalent bond, a carbonyl, an oxygen, -S(O)_o- or -N(R_e) R_f -;

o is an integer from 0 to 2;

R_e is a lone pair of electrons, a hydrogen or an alkyl group;

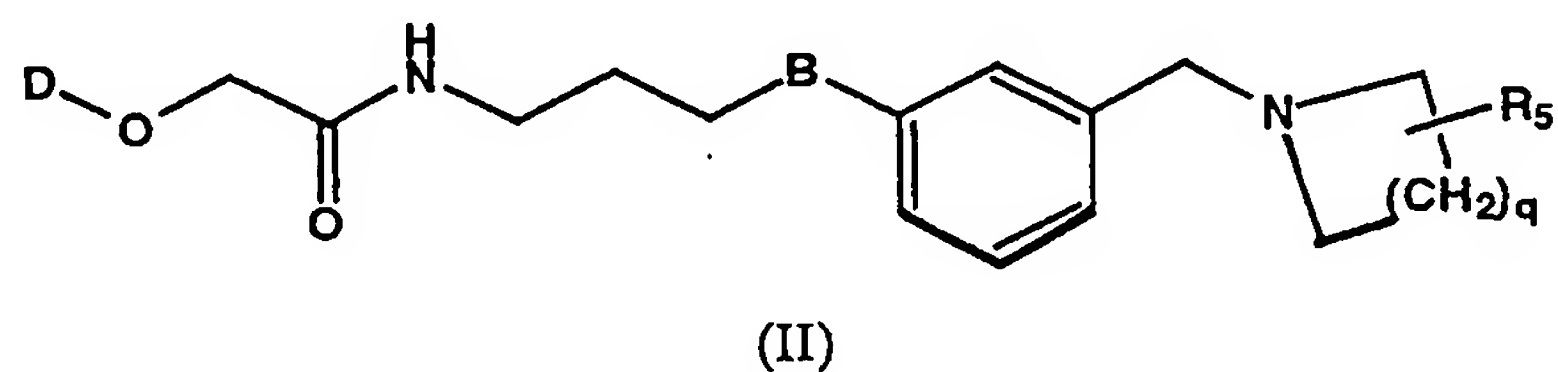
R_f is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, -CH₂-C(T-Q)(R_e)(R_f), or $-(N_2O_2)^- \cdot M^+$, wherein M^+ is an organic or inorganic cation; with the proviso that when R_e is -CH₂-C(T-Q)(R_e)(R_f) or $-(N_2O_2)^- \cdot M^+$, or R_e or R_f are T-Q or $(C(R_e)(R_f))_k$ -T-Q, then the "-T-Q" subgroup designated in X can be a hydrogen, an alkyl, an alkoxy, an alkoxyalkyl, an aminoalkyl, a hydroxy, a heterocyclic ring or an aryl group.

In cases where R_e and R_f are a heterocyclic ring or taken together R_e and R_f are a heterocyclic ring, then R_f can be a substituent on any disubstituted nitrogen contained within the radical where R_e is as defined herein.

In cases where multiple designations of variables which reside in sequence

are chosen as a "covalent bond" or the integer chosen is 0, the intent is to denote a single covalent bond connecting one radical to another. For example, E_0 would denote a covalent bond, while E_2 denotes (E-E) and $(C(R_e)(R_f))_2$ denotes $-C(R_e)(R_f)-C(R_e)(R_f)-$.

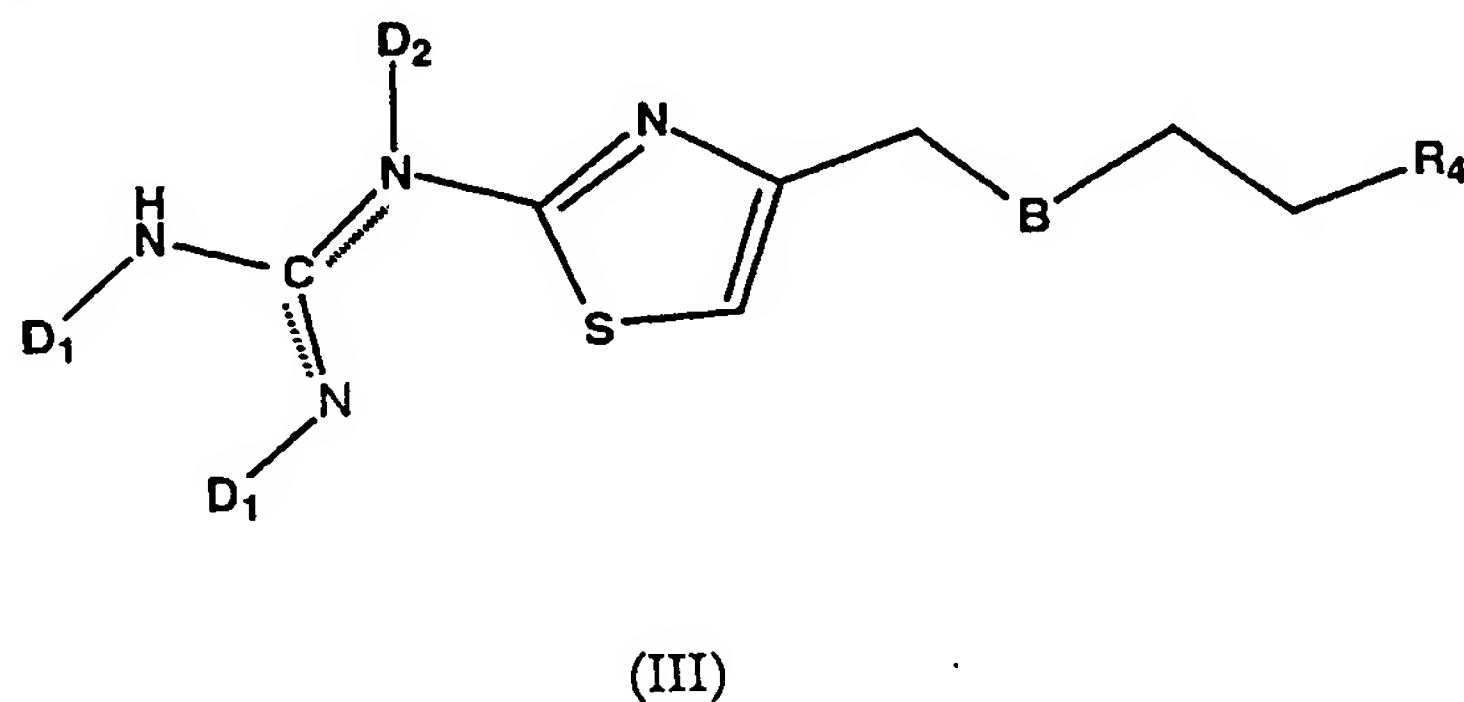
5 Another embodiment of the present invention describes nitrosated and/or nitrosylated compounds of the Formula (II):



10 wherein

R_5 is a hydrogen atom, a hydroxy group or a hydroxyalkyl group; and q , B and D are as defined herein.

Another embodiment of the present invention describes nitrosated and/or nitrosylated compounds of Formula (III):

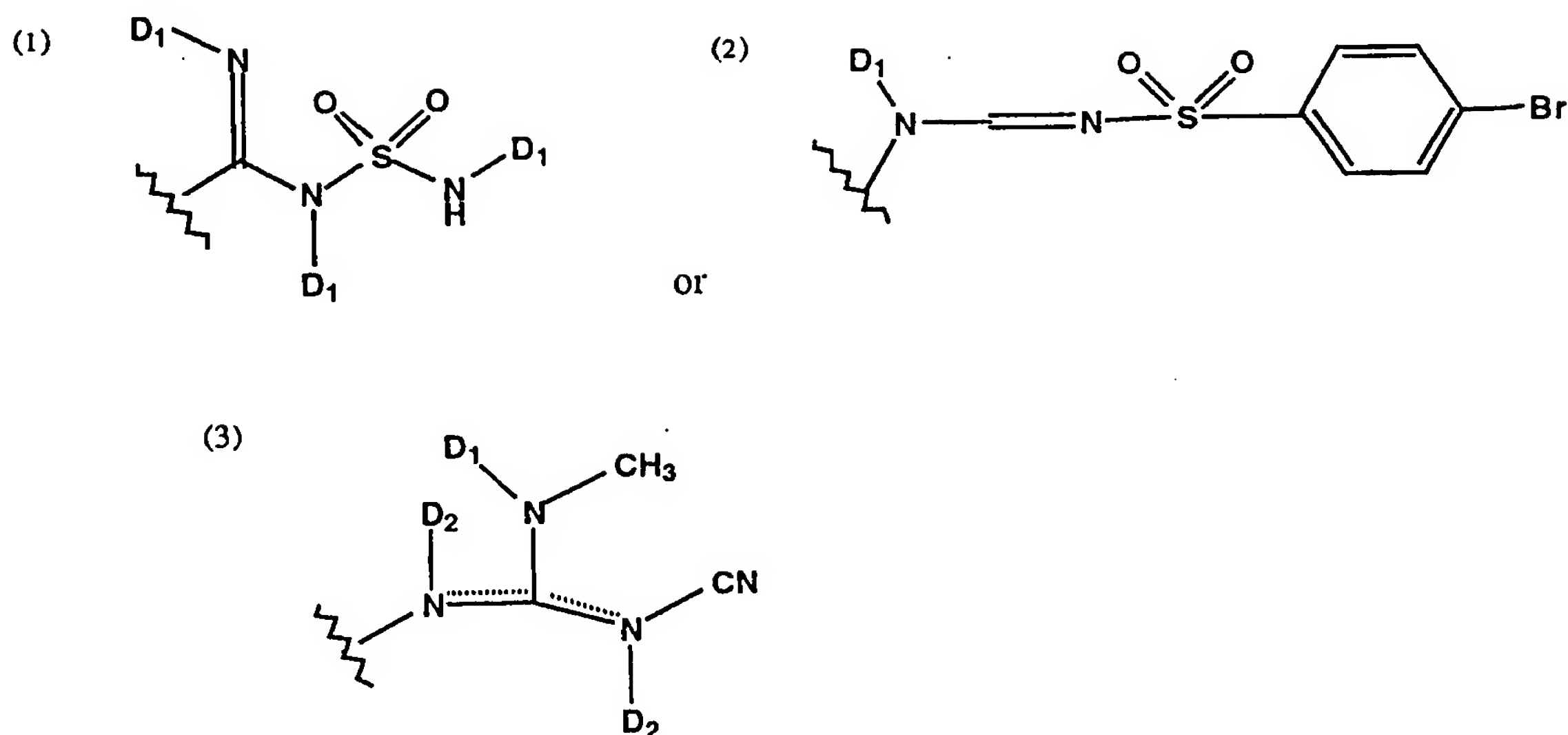


15

wherein

D_2 is D_1 or a lone pair of electrons;

R₁ is:



B, D and D₁ are as defined herein, with the proviso that at least one D₁ must be D, and D is as defined herein.

5 Compounds of the present invention that have one or more asymmetric carbon atoms may exist as the optically pure enantiomers, pure diastereomers, mixtures of enantiomers, mixtures of diastereomers, racemic mixtures of enantiomers, diastereomeric racemates or mixtures of diastereomeric racemates. The present invention includes within its scope all such isomers and mixtures thereof.

10 The present invention includes within its scope compounds which may exist in more than one resonance form and the effect that may have on the positions at D₁ substituents designated in the above structures. The invention also includes within its scope the regiomers of the double bonds of the substituted guanidino or amidino groups.

15 Another aspect of the present invention provides processes for making the novel compounds of the invention and to the intermediates useful in such processes. The compounds of Formulas (I), (II) and (III) can be synthesized by one skilled in the art following the methods and examples described herein. For example, the compounds of the invention can be synthesized as shown in Figs. 1-6,

20

in which A, B, D, D₁, E, K, Q, T, W, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R_e, R_f, a, b, c, d, g, i, j, p, q, x, y and z are as defined herein or as depicted in the reaction schemes for Formulas (I)-(III); P¹ is an oxygen protecting group; and P² is a sulfur protecting group. The reactions are performed in solvents appropriate to the reagents and materials used are suitable for the transformations being effected. It is understood by one skilled in the art of organic synthesis that the functionality present in the molecule must be consistent with the chemical transformation proposed. This will, on occasion, necessitate judgment by the routineer as to the order of synthetic steps, protecting groups required, and deprotection conditions. Substituents on the starting materials may be incompatible with some of the reaction conditions required in some of the methods described, but alternative methods and substituents compatible with the reaction conditions will be readily apparent to one skilled in the art. The use of sulfur and oxygen protecting groups is well known for protecting thiol and alcohol groups against undesirable reactions during a synthetic procedure and many such protecting groups are known and described by, for example, Greene and Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York (1991).

The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by one skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to one skilled in the art, *e.g.*, by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

Nitroso compounds of formula (I), wherein R₁, R₂, R₃, R₆, R₇, R₈ and R₉ are as defined herein, and a nitrite containing acyl group is representative of the D₁ group as defined herein can be prepared as outlined in Fig. 1. The synthesis of acylated prodrugs of substituted guanidines is well known in the art. EP 743320 and WO

97/33576, the disclosures of each of which are incorporated by reference herein in their entirety, describe the preparation of acylguanidine and acylamidine derivatives as thrombin inhibitor prodrugs. The guanidino derivative of structure 1 is converted to the acylated guanidino derivative of structure 2 wherein R is

5 $-W_{a,1}-E_b-(C(R_e)(R_f))_p-E_c-(C(R_e)(R_f))_x-W_d-(C(R_e)(R_f))_y-W_i-E_j-W_g-(C(R_e)(R_f))_z-T-Q$ by reaction with an appropriate protected alcohol containing acid wherein P^1 is as defined herein. Preferred methods for the preparation of acylated guanidino derivatives are initially forming the mixed anhydride via reaction of the protected alcohol containing acid with a chloroformate, such as isobutylchloroformate, in the

10 presence of a non-nucleophilic base, such as triethylamine, in an anhydrous inert solvent, such as dichloromethane, diethylether or THF. The mixed anhydride is then reacted with the guanidino derivative, preferably in the presence of a condensation catalyst, such as 4-dimethyl-amino pyridine (DMAP). Alternatively, the protected alcohol containing acid can first be converted to the acid chloride by

15 treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the guanidino derivative, preferably in the presence of a condensation catalyst, such as DMAP, and a tertiary amine base, such as triethylamine, to produce the acylated guanidino derivative. Alternatively, the protected alcohol containing acid can be coupled to produce the acylated guanidino

20 derivative by treatment with a dehydration agent, such as dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), with a condensation catalyst, such as DMAP. Alternatively, the acylating agent may be reacted with the preformed anion of the guanidino functionality prepared by deprotonating the guanidino group with a strong base such as sodium

25 hydride, lithium hexamethyldisilazide or potassium t-butoxide in an inert solvent such as THF. Preferred protecting groups for the alcohol moiety are silyl ethers, such as a trimethylsilyl or a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent, such as

30 thionyl chloride nitrite, thionyl dinitrite or nitrosium tetrafluoroborate, in a suitable anhydrous solvent, such as dichloromethane, THF, DMF or acetonitrile, with or without an amine base, such as pyridine or triethylamine, produces the compounds of structure IA.

Nitroso compounds of formula (I) wherein R_1 , R_2 , R_3 , R_6 , R_7 , R_8 and R_9 are as defined herein and a nitrosothiol containing acyl group is representative of the D_1 group as defined herein can be prepared as outlined in Fig. 2. The guanidino derivative group of structure 1 is converted to the acylated guanidino derivative of structure 3 by reaction with an appropriate protected thiol containing acid wherein R and P^2 are as defined herein. Preferred methods for the preparation of acylated guanidino derivatives are initially forming the mixed anhydride via reaction of the acid with a chloroformate, such as isobutylchloroformate, in the presence of a non-nucleophilic base, such as triethylamine, in an anhydrous inert solvent, such as dichloromethane, diethylether or THF. The mixed anhydride is then reacted with the guanidino derivative, preferably in the presence of a condensation catalyst, such as DMAP. Alternatively, the acid can first be converted to the acid chloride by treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the guanidino derivative preferably in the presence of a condensation catalyst, such as DMAP, and a tertiary amine base, such as triethylamine, to produce the acylated guanidino derivative. Alternatively, the protected thiol containing acid and guanidino derivative can be coupled to produce the acylated guanidino derivative by treatment with a dehydration agent, such as DCC or EDC, with a condensation catalyst, such as DMAP. Alternatively, the acylating agent may be reacted with the preformed anion of the guanidino functionality prepared by deprotonating the guanidino group with a strong base such as sodium hydride, lithium hexamethyldisilazide or potassium t-butoxide in an inert solvent such as THF. Preferred protecting groups for the thiol moiety are as a thioester, such as thioacetate or thiobenzoate, as a disulfide, as a thiocarbamate, such as N-methoxy-methyl thiocarbamate, or as a thioether, such as paramethoxybenzyl thioether, a 2,4,6-trimethoxybenzyl thioether, a tetrahydropyranyl thioether, or a S-triphenylmethyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenyl-phosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically used to hydrolyze thioesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a 2,4,6-trimethoxybenzyl thioether a tetrahydropyranyl thioether or a S-triphenylmethyl thioether group)

followed by reaction with a suitable nitrosylating agent, such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite, such as tert-butyl nitrite, or nitrosium tetrafluoro-borate, in a suitable anhydrous solvent, such as methylene chloride, THF, DMF or acetonitrile, with or without an amine base, such as pyridine or triethylamine, produces the compounds of structure IB. Alternatively, a stoichiometric quantity of sodium nitrite in alcoholic or aqueous acid produces the compounds of structure IB.

Nitroso compounds of formula (II) wherein B, R₅ and q are as defined herein and a nitrite containing acyl group is representative of the D group as defined herein can be prepared as outlined in Fig. 3. The alcohol of structure 4 is converted to the ester of structure 5 by reaction with an appropriate protected alcohol containing acid wherein R and P¹ are as defined herein. Preferred methods for the preparation of esters are initially forming the mixed anhydride via reaction of the acid with a chloroformate, such as isobutylchloroformate, in the presence of a non-nucleophilic base, such as triethylamine, in an anhydrous inert solvent, such as dichloromethane, diethylether or THF. The mixed anhydride is then reacted with the alcohol, preferably in the presence of a condensation catalyst, such as DMAP. Alternatively, the acid can first be converted to the acid chloride by treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the hydroxyl group, preferably in the presence of a condensation catalyst, such as DMAP, and a tertiary amine base, such as triethylamine, to produce the ester. Alternatively, the protected alcohol containing acid can be coupled to produce the ester by treatment with a dehydration agent, such as DCC or EDC, with or without a condensation catalyst, such as DMAP. Preferred protecting groups for the alcohol moiety are silyl ethers, such as a trimethylsilyl or a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent, such as thionyl chloride nitrite, thionyl dinitrite or nitrosium tetrafluoroborate, in a suitable anhydrous solvent, such as dichloromethane, THF, DMF or acetonitrile, with or without an amine base, such as pyridine or triethylamine, produces the compounds of formula IIA.

Nitroso compounds of formula (II) wherein B, R₅ and q are as defined herein and a nitrosothiol containing acyl group is representative of the D group as defined

herein can be prepared as outlined in Fig. 4. The alcohol of structure 4 is converted to the ester of structure 6 by reaction with an appropriate protected thiol containing acid wherein R and P² are as defined herein. Preferred methods for the preparation of esters are initially forming the mixed anhydride via reaction of the acid with a chloroformate, such as isobutylchloroformate, in the presence of a non-nucleophilic base, such as triethylamine, in an anhydrous inert solvent, such as dichloromethane, diethylether or THF. The mixed anhydride is then reacted with the hydroxyl group, preferably in the presence of a condensation catalyst, such as DMAP. Alternatively, the acid can first be converted to the acid chloride by treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the hydroxyl moiety, preferably in the presence of a condensation catalyst, such as DMAP, and a tertiary amine base, such as triethylamine, to produce the ester. Alternatively, the protected thiol containing acid and alcohol can be coupled to produce the ester by treatment with a dehydration agent, such as DCC or EDC with or without a condensation catalyst such as DMAP. Preferred protecting groups for the thiol moiety are as a disulfide, or as a thioether, such as paramethoxybenzyl thioether, a 2,4,6-trimethoxybenzyl thioether, a tetrahydropyranyl thioether, or a S-triphenylmethyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenyl-phosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while mercuric trifluoroacetate, silver nitrate or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a 2,4,6-trimethoxybenzyl thioether a tetrahydro-pyranyl thioether or a S-triphenylmethyl thioether group) followed by reaction with a suitable nitrosylating agent, such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite, such as tert-butyl nitrite, or nitrosium tetrafluoroborate, in a suitable anhydrous solvent, such as methylene chloride, THF, DMF or acetonitrile, with or without an amine base, such as pyridine or triethylamine, produces the compounds of structure IIB. Alternatively, a stoichiometric quantity of sodium nitrite in alcoholic or aqueous acid produces the compounds of structure IIB.

Nitroso compounds of formula (III) wherein B and R₄ are as defined herein and a nitrite containing acyl group is representative of the D₁ group as defined herein can be prepared as outlined in Fig. 5. The guanidino derivative of formula 7

is converted to the acylated guanidino derivative of structure 8 by reaction with an appropriate protected alcohol containing acid wherein R and P¹ are as defined herein. Preferred methods for the preparation of acylated guanidino derivatives are initially forming the mixed anhydride via reaction of the protected alcohol
5 containing acid with a chloroformate, such as isobutylchloroformate, in the presence of a non-nucleophilic base, such as triethylamine, in an anhydrous inert solvent, such as dichloromethane, diethylether or THF. The mixed anhydride is then reacted with the guanidino derivative, preferably in the presence of a condensation catalyst, such as DMAP. Alternatively, the protected alcohol
10 containing acid can first be converted to the acid chloride by treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the guanidino derivative, preferably in the presence of a condensation catalyst, such as DMAP, and a tertiary amine base, such as triethylamine, to produce the acylated guanidino derivative. Alternatively, the protected alcohol
15 containing acid can be coupled to produce the acylated guanidino derivative by treatment with a dehydration agent, such as DCC or EDC, with or without a condensation catalyst, such as DMAP. Alternatively, the acylating agent may be reacted with the preformed anion of the guanidino functionality prepared by deprotonating the guanidino group with a strong base such as sodium hydride,
20 lithium hexamethyldisilazide or potassium t-butoxide in an inert solvent such as THF. Preferred protecting groups for the alcohol moiety are silyl ethers, such as a trimethylsilyl or a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent, such as thionyl
25 chloride nitrite, thionyl dinitrite or nitrosium tetrafluoroborate, in a suitable anhydrous solvent, such as dichloromethane, THF, DMF or acetonitrile, with or without an amine base, such as pyridine or triethylamine, produces the compounds of structure IIIA.

Nitroso compounds of formula (III) wherein B and R₄ are as defined herein
30 and a nitrosothiol containing acyl group is representative of the D₁ group as defined herein can be prepared as outlined in Fig. 6. The guanidino derivative group of structure 7 is converted to the acylated guanidino derivative of structure 9 by reaction with an appropriate protected thiol containing acid wherein R and P² are as

defined herein. Preferred methods for the preparation of acylated guanidino derivatives are initially forming the mixed anhydride via reaction of the acid with a chloroformate, such as isobutylchloroformate, in the presence of a non-nucleophilic base, such as triethylamine, in an anhydrous inert solvent, such as
5 dichloromethane, diethylether or THF. The mixed anhydride is then reacted with the guanidino derivative, preferably in the presence of a condensation catalyst, such as DMAP. Alternatively, the acid can first be converted to the acid chloride by treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the guanidino derivative preferably in the
10 presence of a condensation catalyst, such as DMAP, and a tertiary amine base, such as triethylamine, to produce the acylated guanidino derivative. Alternatively, the protected thiol containing acid and guanidino derivative can be coupled to produce the acylated guanidino derivative by treatment with a dehydration agent, such as DCC or EDC with or without a condensation catalyst such as DMAP.
15 Alternatively, the acylating agent may be reacted with the preformed anion of the guanidino functionality prepared by deprotonating the guanidino group with a strong base such as sodium hydride, lithium hexamethyldisilazide or potassium t-butoxide in an inert solvent such as THF. Preferred protecting groups for the thiol moiety are as a thioester, such as thioacetate or thiobenzoate, as a disulfide, as a
20 thiocarbamate, such as N-methoxy-methyl thiocarbamate, or as a thioether, such as paramethoxybenzyl thioether, a 2,4,6-trimethoxybenzyl thioether, a tetrahydropyranyl thioether, or a S-triphenylmethyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenyl-phosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous
25 base is typically used to hydrolyze thioesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a 2,4,6-trimethoxybenzyl thioether a tetrahydropyranyl thioether or a S-triphenylmethyl thioether group) followed by reaction with a suitable nitrosylating
30 agent, such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite, such as tert-butyl nitrite, or nitrosium tetrafluoro-borate, in a suitable anhydrous solvent, such as methylene chloride, THF, DMF or acetonitrile, with or without an amine base, such as pyridine or triethylamine, produces the compounds of structure IIIB.

Alternatively, a stoichiometric quantity of sodium nitrite in alcoholic or aqueous acid produces the compounds of structure IIIB.

The compounds of the present invention include H_2 receptor antagonists, such as those described herein, which have been nitrosylated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation), carbon and/or nitrogen. The nitrosated and/or nitrosylated H_2 receptor antagonists of the present invention are capable of donating, transferring and/or releasing a biologically active form of nitrogen monoxide (i.e., nitric oxide).

Nitrogen monoxide can exist in three forms: NO^- (nitroxyl), NO^\bullet (uncharged nitric oxide) and NO^+ (nitrosonium). NO^\bullet is a highly reactive short-lived species that is potentially toxic to cells. This is critical because the pharmacological efficacy of NO depends upon the form in which it is delivered. In contrast to the nitric oxide radical (NO^\bullet), nitrosonium (NO^+) does not react with O_2 or O_2^- species, and functionalities capable of transferring and/or releasing NO^+ and NO^- are also resistant to decomposition in the presence of many redox metals. Consequently, administration of charged NO equivalents (positive and/or negative) is a more effective means of delivering a biologically active NO to the desired site of action.

Compounds contemplated for use in the present invention (e.g., H_2 receptor antagonists optionally substituted with one or more NO and/or NO_2 groups) are, optionally, used in combination with nitric oxide and compounds that release nitric oxide or otherwise directly or indirectly deliver or transfer a biologically active form of nitrogen monoxide to a site of its intended activity, such as on a cell membrane *in vivo*.

The term "nitric oxide" encompasses uncharged nitric oxide (NO^\bullet) and charged nitrogen monoxide species, preferably charged nitrogen monoxide species, such as nitrosonium ion (NO^+) and nitroxyl ion (NO^-). The reactive form of nitric oxide can be provided by gaseous nitric oxide. The nitrogen monoxide releasing, delivering or transferring compounds have the structure F-NO, wherein F is a nitrogen monoxide releasing, delivering or transferring moiety, and include any and all such compounds which provide nitrogen monoxide to its intended site of action in a form active for its intended purpose. The term "NO adducts" encompasses any nitrogen monoxide releasing, delivering or transferring

compounds, including, for example, S-nitrosothiols, nitrites, nitrates, S-nitrothiols, sydnonimines, 2-hydroxy-2-nitrosohydrazines (NONOates), (E)-alkyl-2-[(E)-hydroxyimino]-5-nitro-3-hexene amines or amides, nitrosoamines, furoxans as well as substrates for the endogenous enzymes which synthesize nitric oxide. The "NO
5 adducts" can be mono-nitrosylated, poly-nitrosylated, mono-nitrosated and/or poly-nitrosated or a combination thereof at a variety of naturally susceptible or artificially provided binding sites for biologically active forms of nitrogen monoxide.

One group of NO adducts is the S-nitrosothiols, which are compounds that
10 include at least one -S-NO group. These compounds include S-nitroso-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); S-nitrosylated amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures and derivatives thereof); S-nitrosylated sugars;
15 S-nitrosylated, modified and unmodified, oligonucleotides (preferably of at least 5, and more preferably 5-200 nucleotides); straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted S-nitrosylated hydrocarbons; and S-nitroso heterocyclic compounds. S-nitrosothiols and methods for preparing them are described in U.S. Patent Nos. 5,380,758 and 5,703,073; WO
20 97/27749; WO 98/19672; and Oae et al, *Org. Prep. Proc. Int.*, 15(3):165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety.

Another embodiment of the present invention is S-nitroso amino acids where the nitroso group is linked to a sulfur group of a sulfur-containing amino acid or derivative thereof. Such compounds include, for example, S-nitroso-N-
25 acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine and S-nitroso-glutathione.

Suitable S-nitrosylated proteins include thiol-containing proteins (where the NO group is attached to one or more sulfur groups on an amino acid or amino acid derivative thereof) from various functional classes including enzymes, such as
30 tissue-type plasminogen activator (TPA) and cathepsin B; transport proteins, such as lipoproteins; heme proteins, such as hemoglobin and serum albumin; and biologically protective proteins, such as immunoglobulins, antibodies and cytokines. Such nitrosylated proteins are described in WO 93/09806, the disclosure

of which is incorporated by reference herein in its entirety. Examples include polynitrosylated albumin where one or more thiol or other nucleophilic centers in the protein are modified.

Other examples of suitable S-nitrosothiols include:

- 5 (i) $\text{HS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{SNO}$;
 - (ii) $\text{ONS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{R}_e$; and
 - (iii) $\text{H}_2\text{N}-\text{CH}(\text{CO}_2\text{H})-(\text{CH}_2)_m-\text{C}(\text{O})\text{NH}-\text{CH}(\text{CH}_2\text{SNO})-\text{C}(\text{O})\text{NH}-\text{CH}_2-\text{CO}_2\text{H}$;
- wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylaryl amino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an alkoxy, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkyl carboxamido, an aryl carboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a carbamoyl, a urea, a nitro, -T-Q, or $(\text{C}(\text{R}_e)(\text{R}_f))_k-\text{T}-\text{Q}$, or R_e and R_f taken together are a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or -NO₂; and T is independently a covalent bond, a carbonyl, an oxygen, -S(O)_o- or -N(R_s)R_t-, wherein o is an integer from 0 to 2; k is an integer from 1 to 3; R_s is a lone pair of electrons, a hydrogen or an alkyl group; R_t is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, -CH₂-C(T-Q)(R_e)(R_f), or -(N₂O₂)⁻•M⁺, wherein M⁺ is an organic or inorganic cation; with the proviso that when R_f is -CH₂-C(T-Q)(R_e)(R_f) or -(N₂O₂)⁻•M⁺; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

In cases where R_e and R_f are a heterocyclic ring or taken together R_e and R_f are a heterocyclic ring, then R_f can be a substituent on any disubstituted nitrogen

contained within the radical wherein R_1 is as defined herein.

Nitrosothiols can be prepared by various methods of synthesis. In general, the thiol precursor is prepared first, then converted to the S-nitrosothiol derivative by nitrosation of the thiol group with NaNO_2 under acidic conditions (pH is about 2.5) which yields the S-nitroso derivative. Acids which can be used for this purpose include aqueous sulfuric, acetic and hydrochloric acids. The thiol precursor can also be nitrosylated by reaction with an organic nitrite such as tert-butyl nitrite, or a nitrosonium salt such as nitrosonium tetrafluoroborate in an inert solvent.

Another group of NO adducts for use in the present invention, where the NO adduct is a compound that donates, transfers or releases nitric oxide, include compounds comprising at least one ON-O-, ON-N- or ON-C- group. The compounds that include at least one ON-O-, ON-N- or ON-C- group are preferably ON-O-, ON-N- or ON-C-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); ON-O-, ON-N- or ON-C-amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); ON-O-, ON-N- or ON-C-sugars; ON-O-, ON-N- or ON-C- modified or unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); ON-O-, ON-N- or ON-C- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and ON-O-, ON-N- or ON-C-heterocyclic compounds.

Another group of NO adducts for use in the present invention include nitrates that donate, transfer or release nitric oxide, such as compounds comprising at least one $\text{O}_2\text{N-O-}$, $\text{O}_2\text{N-N-}$, $\text{O}_2\text{N-S-}$ or $\text{O}_2\text{N-C-}$ group. Preferred among these compounds are $\text{O}_2\text{N-O-}$, $\text{O}_2\text{N-N-}$, $\text{O}_2\text{N-S-}$ or $\text{O}_2\text{N-C-}$ polypeptides (the term "polypeptide" includes proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof); $\text{O}_2\text{N-O-}$, $\text{O}_2\text{N-N-}$, $\text{O}_2\text{N-S-}$ or $\text{O}_2\text{N-C-}$ amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); $\text{O}_2\text{N-O-}$, $\text{O}_2\text{N-N-}$, $\text{O}_2\text{N-S-}$ or $\text{O}_2\text{N-C-}$ sugars; $\text{O}_2\text{N-O-}$, $\text{O}_2\text{N-N-}$, $\text{O}_2\text{N-S-}$ or $\text{O}_2\text{N-C-}$ modified and unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); $\text{O}_2\text{N-O-}$, $\text{O}_2\text{N-N-}$, $\text{O}_2\text{N-S-}$ or $\text{O}_2\text{N-C-}$ straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and $\text{O}_2\text{N-O-}$, $\text{O}_2\text{N-N-}$, $\text{O}_2\text{N-S-}$

or O_2N-C - heterocyclic compounds. Preferred examples of compounds comprising at least one O_2N-O -, O_2N-N -, O_2N-S - or O_2N-C - group include isosorbide dinitrate, isosorbide mononitrate, clonitrate, erythrityltetranitrate, mannitol hexanitrate, nitroglycerin, pentaerythritoltetranitrate, pentrinitrol and propatyl nitrate.

5 Another group of NO adducts are N-oxo-N-nitrosoamines that donate, transfer or release nitric oxide and are represented by the formula: $R^1R^2-N(O-M^+)-NO$, where R^1 and R^2 are each independently a polypeptide, an amino acid, a sugar, a modified or unmodified oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted
10 hydrocarbon, or a heterocyclic group, and where M^+ is an organic or inorganic cation, such as, for example, an alkyl substituted ammonium cation or a Group I metal cation.

Another group of NO adducts are thionitrates that donate, transfer or release nitric oxide and are represented by the formula: $R^1-(S)-NO_2$, where R^1 is a
15 polypeptide, an amino acid, a sugar, a modified or unmodified oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group. Preferred are those compounds where R^1 is a polypeptide or hydrocarbon with a pair or pairs of thiols that are sufficiently structurally proximate, i.e., vicinal, that the pair of thiols will be
20 reduced to a disulfide. Compounds which form disulfide species release nitroxyl ion (NO^-) and uncharged nitric oxide (NO^\bullet). Compounds where the thiol groups are not sufficiently close to form disulfide bridges generally provide nitric oxide as the NO^- form and not as the uncharged NO^\bullet form.

The present invention is also directed to compounds that stimulate
25 endogenous NO or elevate levels of endogenous endothelium-derived relaxing factor (EDRF) *in vivo* or are substrates for nitric oxide synthase. Such compounds include, for example, L-arginine, L-homoarginine, and N-hydroxy-L-arginine, including their nitrosated and nitrosylated analogs (e.g., nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-
30 L-arginine, nitrosated L-homoarginine and nitrosylated L-homoarginine), precursors of L-arginine and/or physiologically acceptable salts thereof, including, for example, citrulline, ornithine or glutamine, inhibitors of the enzyme arginase (e.g., N-hydroxy-L-arginine and 2(S)-amino-6-boronohexanoic acid) and the

substrates for nitric oxide synthase, cytokines, adenosin, bradykinin, calreticulin, bisacodyl, and phenolphthalein. EDRF is a vascular relaxing factor secreted by the endothelium, and has been identified as nitric oxide (NO) or a closely related derivative thereof (Palmer et al, *Nature*, 327:524-526 (1987); Ignarro et al, *Proc. Natl. Acad. Sci. USA*, 84:9265-9269 (1987)).

Another aspect of the present invention provides methods to decrease or reverse gastrointestinal toxicity and facilitate ulcer healing resulting from the administration of nonsteroidal antiinflammatory drugs (NSAIDs) to a patient. In particular, the present invention provides methods of administering a therapeutically effective amount of at least one NSAID with a therapeutically effective amount of the compounds and/or compositions described herein. In one aspect of the invention, the patient can be administered at least one NSAID with a therapeutically effective amount of at least one nitrosated and/or nitrosylated H_2 receptor antagonist of the invention to decrease or reverse gastrointestinal toxicity and/or to facilitate ulcer healing resulting from NSAID treatment. In another aspect of the invention, the patient can be administered at least one NSAID with a therapeutically effective amount of at least one nitrosated and/or nitrosylated H_2 receptor antagonist of the invention and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to decrease or reverse gastrointestinal toxicity and/or to facilitate ulcer healing resulting from NSAID treatment. In yet another aspect of the present invention, the patient can be administered at least one NSAID with a therapeutically effective amount of at least one H_2 receptor antagonist and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to decrease or reverse gastrointestinal toxicity and/or to facilitate ulcer healing resulting from NSAID treatment. The NSAID, nitrosated and/or nitrosylated H_2 receptor antagonist, H_2 receptor antagonist, and/or nitric oxide donor can be administered separately or as components of the same composition. These compounds and/or compositions can also be provided in the form of a pharmaceutical kit.

The compounds and compositions of the present invention can be used in this aspect of the invention with any NSAID known in the art. Such NSAIDs

include, for example, aspirin (e.g., acetylsalicylic acid), salicylate esters and salts, acetate esters of salicylic acid, difluorophenyl derivatives (e.g., diflunisal), salicylsalicylic acids (e.g., salsalate), salts of salicylic acids (e.g., sodium salicylate), salicylamide, sodium thiosalicylate, choline salicylate, magnesium salicylate, combinations of choline and magnesium salicylates, 5-aminosalicylic acid (e.g., mesalamine), salicylazosulfapyridine (e.g., sulfasalazine), methylsalicylate, and the like.

Another group of NSAIDs are the pyrazolon derivatives, which include, for example, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, dipyrone and apazone (azapropazone). Another group of NSAIDs are the para-aminophenol derivatives, which are the so-called "coal tar" analgesics, including, for example, phenacetin and its active metabolite acetaminophen. Another group of compounds include indomethacin, a methylated indole derivative, and the structurally related compound sulindac. Yet another group of compounds is the fenamates which are derivatives of N-phenylanthranilic acid (e.g., mefenamic, meclofenamic, flufenamic, tolfenamic and etofenamic acids). Another contemplated NSAID is tolmetin.

Another group of NSAIDs are the propionic acid derivatives. Principal members of this group are, for example, ibuprofen, naproxen, flurbiprofen, fenoprofen and ketoprofen. Other members of this group include, for example, fenbufen, pirprofen, oxaprozin, indoprofen and tiaprofenic acid.

Still other NSAIDs are piroxicam, ampiroxicam, oxicam derivatives (which are a class of antiinflammatory enolic acids), tenoxicam, tenidap, diclofenac (one of the series of phenylacetic acid derivatives that have been developed as antiinflammatory agents). Other NSAIDs include etodolac and nabumentone.

Each of the above contemplated NSAIDs is described more fully in the literature, such as in Goodman and Gilman, *The Pharmacological Basis of Therapeutics* (9th Edition), McGraw-Hill, 1995, Pgs. 617-657; the Merck Index on CD-ROM, Twelfth Edition, Version 12:1, 1996.

Other NSAIDs that can be used in the present invention include those described in U.S. Patent No. 5,703,073, the disclosure of which is incorporated by reference herein in its entirety.

Another aspect of the present invention provides methods to improve the gastroprotective properties, anti-*Helicobacter* properties and antacid properties of H₂

receptor antagonists by administering to a patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. In one aspect of the invention, the patient can be administered at least one nitrosated and/or nitrosylated H_2 receptor antagonist of the invention to improve the gastroprotective properties, anti-*Helicobacter* properties and antacid properties of the H_2 receptor antagonist. In another aspect of the invention, the patient can be administered a bismuth-complex comprising at least one nitrosated and/or nitrosylated H_2 receptor antagonist of the invention to improve the gastroprotective properties, anti-*Helicobacter* properties and antacid properties of the H_2 receptor antagonist. In another aspect of the invention, the patient can be administered at least one nitrosated and/or nitrosylated H_2 receptor antagonist of the invention and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to improve the gastroprotective properties, anti-*Helicobacter* properties and antacid properties of the H_2 receptor antagonist. In another aspect of the invention, the patient can be administered a bismuth complex comprising at least one nitrosated and/or nitrosylated H_2 receptor antagonist of the invention and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to improve the gastroprotective properties, anti-*Helicobacter* properties and antacid properties of the H_2 receptor antagonist. In yet another aspect of the invention, the patient can be administered at least one H_2 receptor antagonist and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to improve the gastroprotective properties, anti-*Helicobacter* properties and antacid properties of the H_2 receptor antagonist. In yet another aspect of the present invention, the patient can be administered a bismuth-complex comprising at least one H_2 receptor antagonist and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to improve the gastroprotective properties, anti-*Helicobacter* properties and antacid properties of the H_2 receptor antagonist.

The bismuth-containing reagent, H_2 receptor antagonist, that is optionally,

substituted with at least one NO and/or NO₂ group, and nitric oxide donor can be administered separately or as components of the same composition. The H₂ receptor antagonists, optionally substituted with at least one NO and/or NO₂ group, and nitric oxide donors are described in detail herein. Bismuth complexes are prepared by boiling the aqueous solution of the free base of the H₂ receptor antagonist with at least one bismuth containing reagent, including, for example, bismuth citrate, bismuth salicylate, bismuth tartaric acid or mixtures thereof.

Another aspect the invention provides methods for preventing or treating gastrointestinal disorders by administering to the patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. Such gastrointestinal disorders include, for example, peptic ulcers, stress ulcers, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, short-bowel (anastomosis) syndrome, hypersecretory states associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia, and bleeding peptic ulcers that result, for example, from neurosurgery, head injury, severe body trauma or burns. In one aspect of the invention, the patient can be administered at least one nitrosated and/or nitrosylated H₂ receptor antagonist of the invention to prevent or treat the gastrointestinal disorder. In another aspect of the invention, the patient can be administered at least one antacid and at least one nitrosated and/or nitrosylated H₂ receptor antagonist of the invention to prevent or treat the gastrointestinal disorder. In another aspect of the invention, the patient can be administered at least one nitrosated and/or nitrosylated H₂ receptor antagonist of the invention and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to prevent or treat the gastrointestinal disorder. In still another aspect of the invention, the patient can be administered at least one antacid, at least one nitrosated and/or nitrosylated H₂ receptor antagonist of the invention, and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to prevent or treat the gastrointestinal disorder. In yet another aspect of the present invention, the patient can be administered at least one H₂ receptor antagonist and at least one compound that donates, transfers or releases nitric

oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to prevent or treat the gastrointestinal disorder. In yet another aspect of the present invention, the patient can be administered at least one antacid, at least one H_2 receptor antagonist, and at least one compound that
5 donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to prevent or treat the gastrointestinal disorder.

The antacid, H_2 antagonist that is optionally substituted with at least one NO and/or NO_2 group, and the nitric oxide donor can be administered separately or as
10 components of the same composition. These compounds and/or compositions can also be provided in the form of a pharmaceutical kit. The H_2 receptor antagonists substituted with at least one NO and/or NO_2 group and preferred nitric oxide donors are described in detail herein. Appropriate antacids for use in this aspect of the invention include any antacid known in the art, including, for example,
15 aluminum hydroxide, magnesium hydroxide, magnesium carbonate, calcium carbonate and co-dried gels, such as, for example, aluminum hydroxide-magnesium carbonate co-dried gel.

Another aspect of the present invention provides methods for preventing and treating inflammations and/or microbial infections by administering the
20 compounds and/or compositions described herein. The inflammations and/or microbial infections that are being prevented or treated are preferably those of the eyes, ears, nose or skin. In one aspect of the invention, the patient can be administered at least one nitrosated and/or nitrosylated H_2 receptor antagonist of the invention to treat the inflammation or microbial infection. In another aspect of
25 the invention, the patient can be administered at least one nitrosated and/or nitrosylated H_2 receptor antagonist of the invention and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to treat the inflammation or microbial infection. In yet another aspect of the present invention, the patient
30 can be administered at least one H_2 receptor antagonist and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to treat the inflammation or microbial infection. The H_2 receptor antagonist that is optionally

substituted with at least one NO and/or NO₂ group and the nitric oxide donor can be administered separately or as components of the same composition.

Another aspect of the present invention provides methods for preventing and treating ophthalmic diseases and disorders by administering the compounds and/or compositions described herein. The ophthalmic diseases and disorders
5 include glaucoma, inflammation of the eye and elevation of intraocular pressure. In one aspect of the invention, the patient can be administered at least one nitrosated and/or nitrosylated H₂ receptor antagonist of the invention to treat the ophthalmic diseases and disorders. In another aspect of the invention, the patient can be
10 administered at least one nitrosated and/or nitrosylated H₂ receptor antagonist of the invention and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to treat the ophthalmic diseases and disorders. In yet another aspect of the present invention, the patient can be administered at least one H₂
15 receptor antagonist and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to treat the ophthalmic diseases and disorders. The H₂ receptor antagonist that is optionally substituted with at least one NO and/or NO₂ group and the nitric oxide donor can be administered separately or as components
20 of the same composition.

Another aspect the present invention provides methods for treating multiple sclerosis, and viral infections, such as HIV disease, by administering to the patient a therapeutically effective amount of the compounds and/or compositions described
25 herein. In one aspect of the invention, the patient can be administered at least one nitrosated and/or nitrosylated H₂ receptor antagonist of the invention to treat multiple sclerosis or the viral infection. Treating a viral infection can further comprise administering at least one anti-viral agent to the patient. In another aspect of the invention, the patient can be administered at least one nitrosated and/or nitrosylated H₂ receptor antagonist of the invention, at least one compound
30 that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to treat multiple sclerosis or the viral infection. Treating a viral infection can further comprise administering at least one anti-viral agent to the patient. In yet another aspect of

the present invention, the patient can be administered at least one H₂ receptor antagonist and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to treat multiple sclerosis or the viral infection. Treating a viral infection can further comprise administering at least one anti-viral agent to the patient.

The H₂ receptor antagonist that is substituted with at least one NO and/or NO₂ group, the anti-viral agents, and the nitric oxide donor can be administered separately or as components of the same composition. The H₂ receptor antagonists substituted with at least one NO and/or NO₂ group and preferred nitric oxide donors are described in detail above. Appropriate anti-viral agents include any anti-viral agent known in the art, including, for example, metronidazole, AZT (3'-azidothymidine), DDI (2',3'-dideoxyinosine), DDC (2',3'-dideoxycytidine), L-735,524 (N-(2-(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(butylcarboxamido)-piperazinyl))-pentaneamide), and the like. These compounds and/or compositions can also be provided in the form of a pharmaceutical kit. Preferred H₂ receptor antagonists, including those that are substituted with at least one NO and/or NO₂ group, and preferred nitric oxide donors are described in detail herein.

When administered *in vivo*, the compounds and compositions of the present invention can be administered in combination with pharmaceutically acceptable carriers and in dosages described herein. While the compounds and compositions of the invention can be administered as a mixture of an H₂ receptor antagonist that is optionally substituted with at least one NO and/or NO₂ group and a nitric oxide donor, they can also be used in combination with one or more additional compounds (e.g., NSAIDs, antacids, bismuth-containing reagents, anti-viral agents) which are known to be effective against the specific disease state that one is targeting for treatment. The nitric oxide donor(s) can be administered simultaneously with, subsequently to, or prior to administration of the H₂ receptor antagonist that is optionally substituted with at least one NO and/or NO₂ group, and/or other additional compounds.

The compounds and compositions of the present invention can be administered by any available and effective delivery system including, but not

limited to, orally, buccally, parenterally, by inhalation spray, by topical application, by injection, transdermally, or rectally (e.g., by the use of suppositories) in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles, as desired. Parenteral includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Transdermal compound administration, which is known to one skilled in the art, involves the delivery of pharmaceutical compounds via percutaneous passage of the compound into the systemic circulation of the patient. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. Other components can be incorporated into the transdermal patches as well. For example, compositions and/or transdermal patches can be formulated with one or more preservatives or bacteriostatic agents including, but not limited to, methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chloride, and the like. Dosage forms for topical administration of the compounds and compositions can include creams, sprays, lotions, gels, ointments, eye drops, nose drops, ear drops, and the like. In such dosage forms, the compositions of the invention can be mixed to form white, smooth, homogeneous, opaque cream or lotion with, for example, benzyl alcohol 1% or 2% (wt/wt) as a preservative, emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water and sorbitol solution. In addition, the compositions can contain polyethylene glycol 400. They can be mixed to form ointments with, for example, benzyl alcohol 2% (wt/wt) as preservative, white petrolatum, emulsifying wax, and tenox II (butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g., gauze, can be impregnated with the compositions in solution, lotion, cream, ointment or other such form can also be used for topical application. The compositions can also be applied topically using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the composition and laminated to an impermeable backing.

Solid dosage forms for oral administration can include capsules, tablets, effervescent tablets, chewable tablets, pills, powders, sachets, granules and gels. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms can also

comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, effervescent tablets, and pills, the dosage forms can also comprise buffering agents. Soft gelatin capsules can be prepared to contain a mixture of the active compounds or compositions of the present invention and vegetable oil. Hard gelatin capsules
5 can contain granules of the active compound in combination with a solid, pulverulent carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives of gelatin. Tablets and pills can be prepared with enteric coatings.

10 Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

15 Suppositories for vaginal or rectal administration of the compounds and compositions of the invention, such as for treating pediatric fever and the like, can be prepared by mixing the compounds or compositions with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at room temperature but liquid at rectal temperature, such that they will melt
20 in the rectum and release the drug.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing agents, wetting agents and/or suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally
25 acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be used are water, Ringer's solution, and isotonic sodium chloride solution. Sterile fixed oils are also conventionally used as a solvent or suspending medium.

The compositions of this invention can further include conventional
30 excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, for example, water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose,

amylose, magnesium stearate, talc, surfactants, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, and the like. The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds. For parenteral application, particularly suitable vehicles consist of solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. Aqueous suspensions may contain substances which increase the viscosity of the suspension and include, for example, sodium carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

The composition, if desired, can also contain minor amounts of wetting agents, emulsifying agents and/or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like.

Various delivery systems are known and can be used to administer the compounds or compositions of the present invention, including, for example, encapsulation in liposomes, microbubbles, emulsions, microparticles, microcapsules and the like.

The bioavailability of the compositions can be enhanced by micronization of the formulations using conventional techniques such as grinding, milling, spray drying and the like in the presence of suitable excipients or agents such as phospholipids or surfactants.

The compounds and compositions of the present invention can be formulated as neutral or pharmaceutically acceptable salt forms. Pharmaceutically acceptable salts include, for example, those formed with free amino groups such as those derived from hydrochloric, hydrobromic, phosphoric, sulfuric, acetic, citric,

benzoic, fumaric, glutamic, lactic, malic, maleic, nitric, succinic, tartaric p-toluene-sulfonic, methanesulfonic, acids, gluconic acid, and the like, and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

"Therapeutically effective amount" refers to the amount of the H₂ receptor antagonist that is optionally substituted with at least one NO and/or NO₂ group and nitric oxide donor that is effective to achieve its intended purpose. While individual patient needs may vary, determination of optimal ranges for effective amounts of each of the compounds and compositions is within the skill of the art. Generally, the dosage required to provide an effective amount of the composition, and which can be adjusted by one of ordinary skill in the art will vary, depending on the age, health, physical condition, sex, weight, extent of the dysfunction of the recipient, frequency of treatment and the nature and scope of the dysfunction or disease.

The amount of a given H₂ receptor antagonist that is optionally substituted with at least one NO and/or NO₂ group which will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques, including reference to Goodman and Gilman, *supra*; The Physician's Desk Reference, Medical Economics Company, Inc., Oradell, N.J., 1995; and Drug Facts and Comparisons, Inc., St. Louis, MO, 1993. The precise dose to be used in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided by the physician and the patient's circumstances.

The amount of nitric oxide donor in a pharmaceutical composition can be in amounts of about 0.1 to about 10 times the molar equivalent of the H₂ receptor antagonist. The usual daily doses of H₂ receptor antagonists are about 1 mg to about 10 g per day and the doses of nitric oxide donors in the pharmaceutical composition can be in amounts of about 0.001 mg to about 40 g, while that actual amount will be dependent upon the specific nitric oxide donor. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems and are in the same ranges or less than as described for the commercially available compounds in the Physician's Desk Reference, *supra*.

The present invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compounds and/or compositions of the present invention, including, at least, one or more of the H_2 receptor antagonists, that are optionally substituted with at least one NO and/or NO_2 group, described herein and one or more of the NO donors described herein. Associated with such kits can be additional compounds or compositions (e.g., NSAIDs, antacids, bismuth-containing reagents, anti-viral agents, permeation enhancers, lubricants, and the like), devices for administering the compositions, and notices in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products which reflects approval by the agency of manufacture, use or sale for humans.

EXAMPLES

The following non-limiting examples further describe and enable one of ordinary skill in the art to make and use the present invention. In each of the examples, flash chromatography was performed on 40 micron silica gel (Baker).

Example 1: (2Z)-2-aza-3-(methylamino)-3-((2-[(5-methyl-1-{2-[2-(nitrosothio)adamantan-2-yl]acetyl}imidazol-4-yl)methylthio]ethyl)amino)prop-2-enenitrile

1a. adamantane-2-thione

Adamantan-2-one (48.46 g, 322.6 mmol) in pyridine (300 mL) was heated to 90°C, and phosphorous pentasulfide (17.84 g, 40.13 mmol) was added. The reaction was maintained at 90°C for two hours, and at room temperature overnight, during which time a precipitate formed. The pyridine solution was decanted and concentrated to dryness. The residual semisolid was treated with hexane (400 mL) to give an orange solution with a light brown suspension. The suspension was removed by filtration. The filtrate was concentrated to dryness and dried under vacuum to give an orange solid (50.36 g). This crude product was purified by filtration through a pad of silica gel (hexane). 1H NMR (300 MHz, $CDCl_3$): δ 3.43 (s, 2H), 2.1-1.9 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 222.4, 57.5, 41.1, 36.5, 27.4.

1b. tert-butyl 2-(2-sulfanyladamantan-2-yl)acetate

To t-butyl acetate (25 mL, 21.6 g, 186 mmol) in dry THF (400 mL) at -78°C was added lithium diisopropylamide monotetrahydrofuran (1.5 M solution in cyclohexane, 100 mL, 150 mmol) under nitrogen. It was stirred at -78°C for 40

minutes. The product of Example 1a (21.88 g, 131.57 mmol) in THF (400 mL) was added. The cold bath was removed and the reaction was stirred at room temperature for two hours. The reaction was diluted with methylene chloride, and 2 M HCl (75 mL) was added. The organic phase was separated, washed with brine (4 x 40 mL), dried (MgSO₄), filtered, and concentrated. The crude product was purified by filtration through a pad of silica gel (5% EtOAc/95% hexane) to give the title compound (34.67 g, 122.7 mmol, 93%). R_f = 0.48 (EtOAc/ hexane 1:19). ¹H NMR (300 MHz, CDCl₃): δ 2.87 (s, 2H), 2.47 (d, J = 11.5, 2H), 2.38 (s, 1H), 2.11 (d, J = 11.9, 2H), 1.98 (s, 2H), 1.96 (m, 2H), 1.84-1.62 96 (m, 6H), 1.47 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): δ 170.8, 80.7, 54.1, 47.3, 39.0, 38.2, 37.2, 36.6, 34.0, 33.3, 28.2, 27.5, 26.9. APIMS (IS, NH₄OAc) m/e 283 (MH⁺). Anal. Calcd. for C₁₆H₂₆O₂S (282.44): C, 68.04; H, 9.28. Found: C, 68.14; H, 9.30.

1c. 2-(2-sulfanyladamantan-2-yl)acetic acid

To the product of Example 1b (10.76 g, 38.1 mmol) in methylene chloride (15 ml) was added trifluoroacetic acid (TFA) (15 mL). The reaction was stirred at room temperature for 40 minutes and concentrated to dryness. The residue was treated with methylene chloride and concentrated to dryness three times. The residual solid was triturated with methylene chloride (20 ml). Solid was collected by filtration, washed with a small amount of methylene chloride, and dried in vacuum to give the title compound (5.6447 g, 24.94 mmol, 65%). ¹H NMR (300 MHz, CDCl₃): δ 9.5 (broad, 1H), 3.04 (s, 2H), 2.49 (d, J = 11.2, 2H), 2.25 (s, 1H), 2.1-2.0 (m, 4H), 1.9 (m, 2H), 1.7-1.6 (m, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 177.7, 53.4, 46.3, 38.9, 37.8, 33.8, 33.2, 27.4, 26.8. APIMS (IS, NH₄OAc) m/e 225 (M-H⁺). Anal. Calcd for C₁₂H₁₈O₂S (226.33): C, 63.68; H, 8.02. Found: C, 63.40; H, 7.90.

1d. 2-[2-(nitrosothio)adamantan-2-yl]acetic acid

The product of Example 1c (773.1 mg, 3.416 mmol) was dissolved in hot methylene chloride (40 mL). The methylene chloride solution was cooled to room temperature and t-butyl nitrite (420 mL, 370 mg, 3.59 mmol) was added. The reaction immediately turned green and was stirred at room temperature for 30 minutes. Some methylene chloride (15 mL) was evaporated at reduced pressure to give a suspension. This suspension was stored in refrigerator over the weekend and purified by column chromatography (silica gel, 25% EtOAc/75% hexane) to give the title compound (628.2 mg, 2.46 mmol, 72%). ¹H NMR (300 MHz, CDCl₃): δ 10.8

(broad, 1H), 3.77 (s, 2H), 2.78 (s, 2H), 2.4 (m, 2H), 2.1-1.7 (m, 10H). ¹³C NMR (75 MHz, CDCl₃): δ 177.0, 65.2, 42.1, 38.8, 35.4, 33.7, 33.1, 27.1. APIMS (IS, NH₄OAc) m/e 254 (M-H).

1e. (2Z)-2-aza-3-(methylamino)-3-({2-[(5-methyl-1-{2-[2-(nitrosothio)-adamantan-2-yl]acetyl}imidazol-4-yl)methylthio]ethyl}amino)prop-2-enenitrile

To an ice-cooled suspension of the product of Example 1d (2.16 g, 8.46 mmol) and (2Z)-2-aza-3-(methylamino)-3-({2-[(5-methylimidazol-4-yl)methylthio]ethyl}amino)prop-2-enenitrile (2.34 g, 9.27 mmol) in dichloromethane (90 mL) was added a solution of 1 M 1,3-dicyclohexylcarbodiimide (DCC) in dichloromethane (10.7 mL, 10.7 mmol). After 30 minutes, the reaction was warmed to room temperature and stirred for 1 hour. To the reaction was added water (100 mL). After separation of layers, the aqueous layer was extracted by dichloromethane (2 x 50 mL). The combined organic layers were dried with sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography (SiO₂, ethyl acetate followed by 3-5% methanol/ethyl acetate). The title compound was obtained as a green foam (1.10 g, 26.5%). R_f = 0.58 (SiO₂, 10% methanol in ethyl acetate); ¹H NMR (300 MHz, CDCl₃): δ 1.79-2.12 (m, 10 H), 2.33 (s, 3H), 2.47 (d, J = 13.1 Hz, 2 H), 2.68 (t, J = 6.4 Hz, 2 H), 2.85 (d, J = 4.0 Hz, 3 H), 2.96 (s, 2H), 3.43 (d, J = 5.7 Hz, 2 H), 3.59 (s, 2 H), 4.40 (s, 2 H), 6.59 (s, 1 H), 6.74 (br s, 1 H), 7.96 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃): δ 11.08, 2.63, 26.67, 28.05, 32.88, 33.28, 35.37, 38.29, 40.91, 42.77, 66.00, 118.86, 125.03, 135.49, 137.06, 160.16, 167.95; LCMS (m/e): 490 (M⁺).

Example 2: (N-{3-[3-(piperidylmethyl)phenoxy]propyl}carbamoyl)methyl 2-[2-(nitrosothio)adamantan-2-yl]acetate

To an ice-cooled solution of the product of Example 1d (0.589 g, 2.31 mmol), 2-hydroxy-N-{3-[3-(piperidylmethyl)phenoxy]propyl}acetamide (0.706 g, 2.30 mmol) and DMAP (10 mg) in dichloromethane (20 mL) was added a solution of 1 M DCC in dichloromethane (2.5 mL, 2.5 mmol). After 30 minutes, the reaction was warmed to room temperature and stirred for 1 hour. The reaction was diluted with dichloromethane (30 mL) and washed with water (30 mL). After drying over sodium sulfate and concentration under vacuum, the residue was purified by flash chromatography (SiO₂, 10% methanol in ethyl acetate) to afford the title compound as a green oil (0.45 g, 35.9%). ¹H NMR (300MHz, CDCl₃): δ 1.30-1.35 (m, 2 H),

1.55-1.60 (m, 4 H), 1.74-2.03 (m, 12 H), 2.34-2.40 (m, 6 H), 2.75 (br s, 2 H), 3.44-3.55 (m, 2 H), 3.46 (s, 2 H), 3.82 (s, 2 H), 4.03 (t, J = 5.9 Hz, H), 4.44 (s, 2 H), 6.39 (br t, J = 5.0 Hz, 1 H), 6.79 (d, J = 7.5 Hz, 1 H), 6.90 (d, J = 7.0 Hz, 1 H), 6.92 (s, 1H), 7.20 (t, J = 7.9 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃): δ 24.03, 25.52, 26.79, 28.61, 32.88, 33.48, 35.34, 36.69, 38.48, 41.83, 54.11, 62.57, 63.34, 65.71, 112.98, 115.07, 121.73, 128.86, 139.64, 158.45, 166.67, 168.77; MS (m/e): 544 (M+).

Example 3: (N-3-{[3-(piperidylmethyl)phenoxy]propyl}carbamoyl)methyl 3-[N-[2-methyl-2-(nitrosothio)propyl]carbamoyl]propanoate

3a. 3-[N-(2-methyl-2-sulfanylpropyl)carbamoyl]propanoic acid

To an ice-cooled suspension of 1-amino-2-methylpropan-2-thiol hydrochloride (5.06 g, 35.72 mmol) in methylene chloride (100 mL) was added triethylamine (5.0 mL, 35.87 mmol) followed by succinic anhydride (3.50 g, 34.96 mmol). The resulting clear solution was stirred at 0 °C for 10 minutes, then at room temperature for 2 hours. Evaporation of the volatiles under reduced pressure gave a residue which was partitioned between 2 N hydrochloric acid (100 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate and evaporated to dryness. The residue was triturated with ether-hexane to afford the title compound as a white solid (6.78 g, 94.4%). Mp. 86-87 °C; ¹H NMR (300 MHz, CDCl₃): δ 1.34 (s, 6H), 1.55 (s, 1H), 2.59 (t, J = 6.6 Hz, H), 2.70 (t, J = 6.6 Hz, 2H), 3.32 (d, J = 8.0 Hz, 2H), 6.58 (br t, J = 5.9 Hz, 1H), 10.73 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 29.57, 29.79, 30.79, 172.50, 176.81; LCMS (m/e): 223 (M+H₂O), 206 (M+1).

3b. (N-3-{[3-(piperidylmethyl)phenoxy]propyl}carbamoyl)methyl 3-[N-(2-methyl-2-sulfanylpropyl)carbamoyl]propanoate

To an ice-cooled solution of 2-hydroxy-N-{3-[3-(piperidylmethyl)phenoxy]propyl}acetamide (1.12 g, 3.66 mmol), the product of Example 3a (0.83 g, 4.04 mmol) and DMAP (30 mg) in dichloromethane (50 mL) was added a solution of 1 M DCC in dichloromethane (4.75 mL, 4.75 mmol). The reaction was stirred at 0 °C for 30 minutes and at room temperature for 2 hours. Additional 2-hydroxy-N-{3-[3-(piperidyl-methyl)phenoxy]propyl}acetamide (0.39 g) and 1 M DCC in dichloromethane (2 mL) was added and stirring was continued for 1 hour. The reaction was washed with water (50 mL) and the aqueous phase was extracted with

dichloromethane (2 x 50 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2 , ethyl acetate, then 10% methanol/ethyl acetate, followed by 1:10:90 triethylamine/methanol/ethyl acetate) to afford the title compound as a viscous oil (1.099 g, 60.9%). ^1H NMR (300 Hz, CDCl_3): δ 1.31 (s, 6 H), 1.33 (s, 1 H), 1.41-1.44 (m, 2 H), 1.53-1.67 (m, 4 H), 2.01-2.07 (m, 2 H), 2.37 (m, 4 H), 2.63 (m, 4 H), 3.27 (d, $J = 6.2$ Hz, 2 H), 3.39 (s, 2 H), 3.47 (q, $J = 6.0$ Hz, 2 H), 4.01 (t, $J = 6.1$ Hz, 2 H), 4.63 (s, 2 H), 6.39 (br t, $J = 5.8$ Hz, 1 H), 6.76 (dd, $J = 7.5$ and 1.9 Hz, 1 H), 6.87 (s, 1 H), 6.89 (d, $J = 6.6$ Hz, 1 H), 7.19 (t, $J = 7.9$ Hz, 1 H), 7.50 (br t, $J = 5.2$ Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ 24.21, 25.81, 28.78, 29.47, 29.82, 30.78, 36.59, 45.09, 52.20, 54.35, 62.73, 63.63, 65.54, 112.73, 115.16, 121.53, 128.89, 140.14, 158.64, 167.52, 171.69, 171.80; MS (m/e): 494 (M^+).

3c. (N-3-{[3-(piperidylmethyl)phenoxy]propyl}carbamoyl)methyl 3-{N-[2-methyl-2-(nitrosothio)propyl]carbamoyl}propanoate

To a solution of the product of Example 3b (0.486 g, 0.98 mmol) in dichloromethane (10 mL) was added a saturated solution of HCl in methanol (2 mL). Tert-butyl nitrite (0.127 mL, 1.08 mmol) was introduced to the reaction which immediately turned greenish. After 30 minutes, the reaction was evaporated under vacuum. The residue was partitioned between aqueous saturated potassium bicarbonate (30 mL) and dichloromethane (30 mL). After separation, the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum to afford the crude product which was purified by flash chromatography (SiO_2 , ethyl acetate, then 10% methanol/ethyl acetate, then 1:10:90 triethylamine /methanol/ethyl acetate). The title compound (0.421 g, 81.8%) was isolated as a green oil. ^1H NMR (300 MHz, CDCl_3): δ 1.34-1.43 (m, 2 H), 1.54-1.57 (m, 4 H), 1.82 (s, 6 H), 2.04-2.07 (m, 2 H), 2.36 (m, 4 H), 2.61 (m, 4 H), 3.43 (s, 2 H), 3.47 (q, $J = 5.9$ Hz, 2 H), 3.96 (d, $J = 6.5$ Hz, 2 H), 4.02 (t, $J = 6.0$ Hz, 2 H), 4.60 (s, 2 H), 6.65 (br t, $J = 5.6$ Hz, 1 H), 6.76 (d, $J = 7.7$ Hz, 1 H), 6.87 (s, 1 H), 6.88 (d, $J = 6.3$ Hz, 1 H), 7.19 (t, $J = 8.0$ Hz, 1 H), 7.52 (br t, $J = 5.2$ Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ 24.16, 25.74, 26.62, 28.75, 29.42, 30.65, 36.61, 49.32, 54.33, 56.94, 62.66, 63.60, 65.50, 112.76, 115.18, 121.58, 128.90, 139.99, 158.63, 167.54, 171.78, 172.12; MS (m/e): 523 (M^+).

Example 4: Comparative *In Vivo* Gastric Lesion Activity

The ethanol/HCl mixture-induced gastric lesion test in rats described by Takeuchi et al, *J. Pharmacol. Exp. Ther.*, 286: 115-121 (1998), was used to evaluate the gastric lesion activity. Male Sprague Dawley rats (Charles River Laboratories, Wilmington, MA) weighing 230-250 g were used for the experiments. The rats were housed with laboratory chow and water *ad libitum* prior to the study. The rats were fasted for 24 hours with free access to water and then dosed by oral gavage with vehicle or with the test compounds given at a volume of 0.5 ml/100 g body weight. Thirty minutes after oral dosing all the rats received 1 ml of a solution of 60% ethanol in 150 mM HCl intragastrically. Food was withheld after dosing. Sixty minutes after ethanol/HCl, rats were euthanized by pre-charged CO₂. The stomachs were dissected along the greater curvature, washed with a directed stream of 0.9% saline and pinned open on a sylgard based petri dish for examination of the hemorrhagic lesions. Gastric lesion score was expressed in mm and calculated by summing the length of each lesion as described by Al-Ghamdi et al, *J. Int. Med. Res.*, 19: 2242 (1991). Results are expressed as the mean \pm standard error of the mean. Statistical analysis were conducted using ANOVA test followed by a Student-Newman-Keuls post-hoc test using the Abacus Concepts, Super Anova computer program (Abacus Concepts, Inc., Berkeley, CA).

Fig. 7 compares the gastric lesion activity of vehicle alone, cimetidine in vehicle and Example 1 (nitrosylated cimetidine) in vehicle. Ethanol/HCl mixture produced gastric lesion in the control rats treated with vehicle (0.5% Methocel). Cimetidine at doses of 160 and 320 μ mol/kg failed to significantly inhibit the formation of gastric lesions. However, Example 1, the nitrosylated cimetidine derivative, at 160 and 320 μ mol/kg significantly inhibited the formation of gastric lesions produced by the ethanol/HCl mixture.

The disclosure of each patent, patent application and publication cited or described in the present specification is hereby incorporated by reference herein in its entirety.

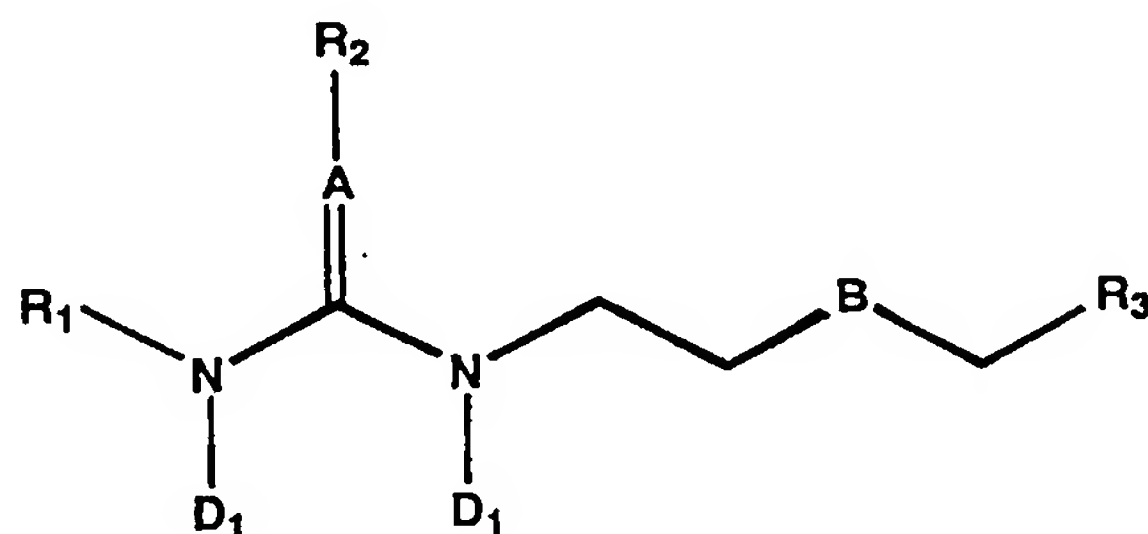
Although the invention has been set forth in detail, one skilled in the art will appreciate that numerous changes and modifications can be made to the invention, and that such changes and modifications can be made without departing from the spirit and scope of the present invention.

CLAIMS

What is claimed is:

1. A compound of formula (I), formula (II) or formula (III), or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is:

5



(I)

wherein

10

A is CH, nitrogen or sulfur;

B is oxygen, S(O)_o or CH₂;

o is an integer from 0 to 2;

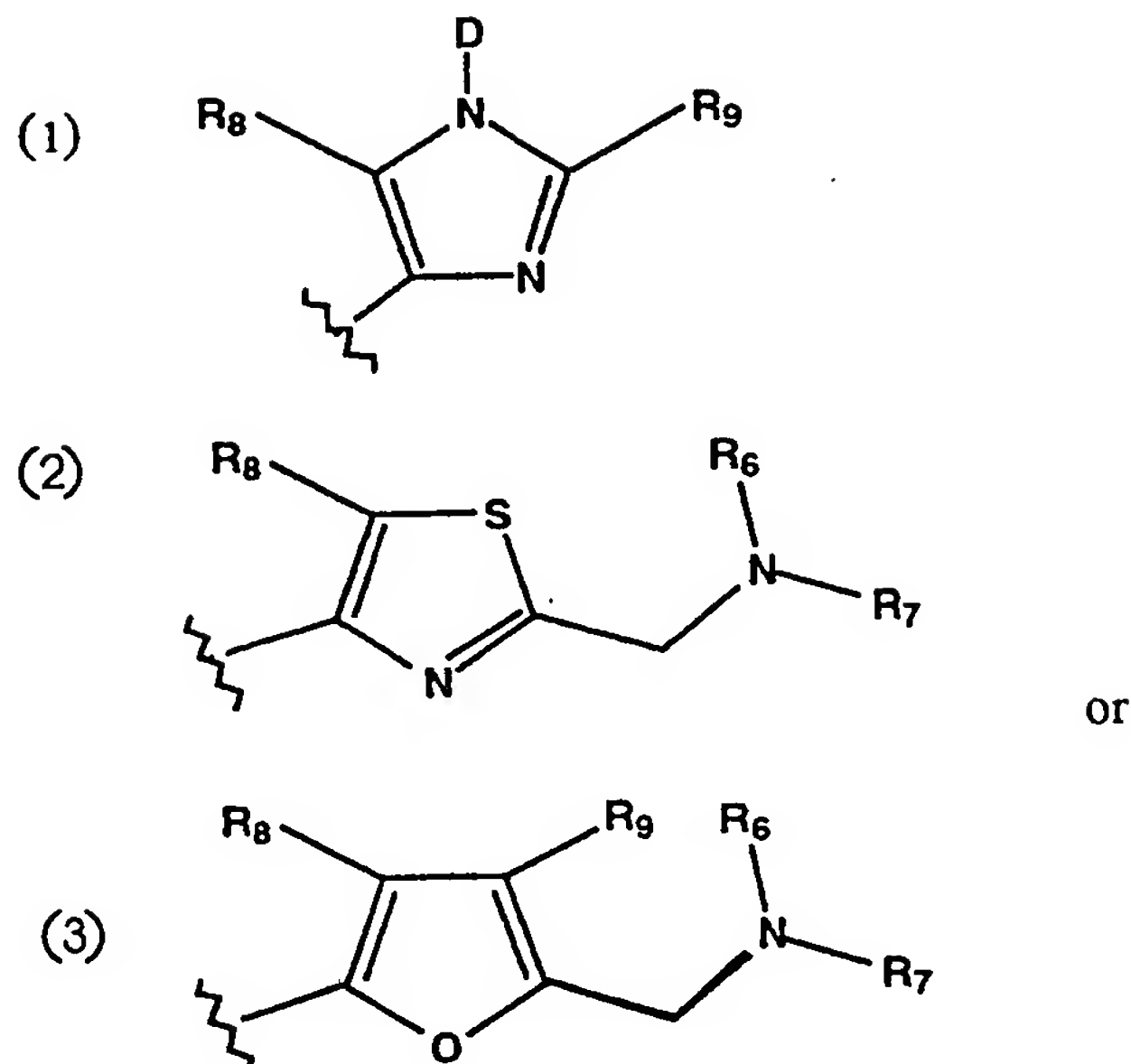
D₁ is a hydrogen atom or D;

R₁ is a hydrogen atom, a lower alkyl group, a cycloalkylalkyl group, a hydroxyalkyl group, an alkoxyalkyl group or an aminoalkyl group;

15

R₂ is a lone pair of electrons, a nitrile group, a nitro group, an alkylsulfonyl group, an arylsulfonyl group, an alkylcarbonyl group, a carboxamido group, a carboxylic ester or a cycloalkylalkyl group;

R_3 is:



with the proviso that at least one D_1 must be D if there is no D designated in the structure;

5 R_6 and R_7 are each independently K, a hydrogen atom, a lower alkyl group, an alkylaryl group, an arylcarbonyl group, an alkylcarbonyl group, or R_6 and R_7 taken together are a heterocyclic ring;

R_8 and R_9 are independently a hydrogen atom or a lower alkyl group;

D is Q or K;

10 Q is -NO or -NO₂;

K is $-W_a-E_b-(C(R_e)(R_f))_p-E_c-(C(R_e)(R_f))_x-W_d-(C(R_e)(R_f))_y-W_i-E_j-W_g-(C(R_e)(R_f))_z-T-Q$;

a, b, c, d, g, i and j are each independently an integer from 0 to 3;

p, x, y and z are each independently an integer from 0 to 10;

15 W at each occurrence is independently -C(O)-, -C(S)-, -T-, $-(C(R_e)(R_f))_h-$, an alkyl group, an aryl group, a heterocyclic ring, an arylheterocyclic ring, or $-(CH_2CH_2O)_q-$;

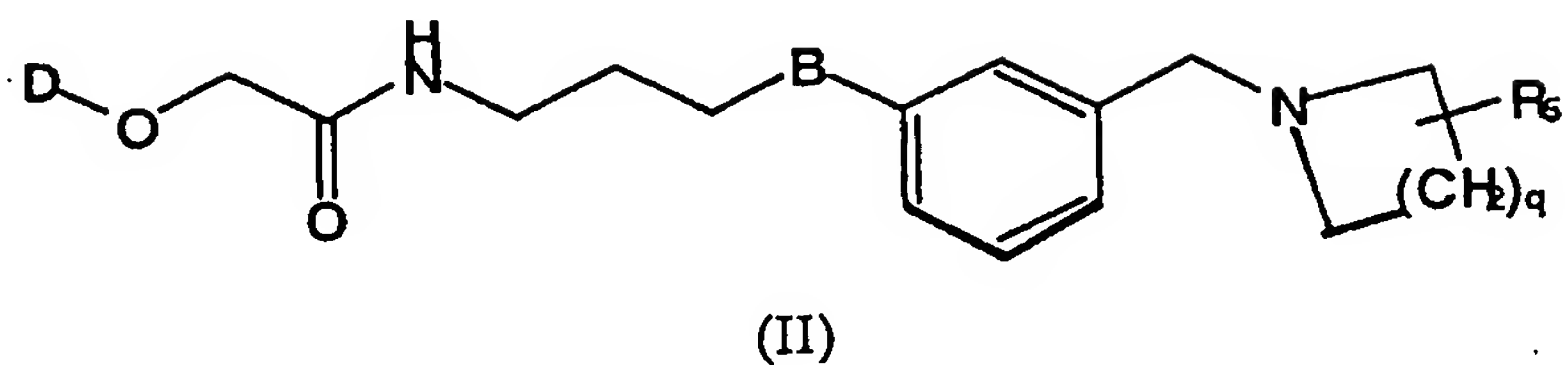
E at each occurrence is independently -T-, an alkyl group, an aryl group, $-(C(R_e)(R_f))_h-$, a heterocyclic ring, an arylheterocyclic ring, or $-(CH_2CH_2O)_q-$;

h is an integer from 1 to 10;

20 q is an integer from 1 to 5;

- R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylaryl amino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an alkoxy, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkyl carboxamido, an aryl carboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a carbamoyl, a urea, a nitro, -T-Q, or $(C(R_e)(R_f))_k$ -T-Q, or R_e and R_f taken together are a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group;
- k is an integer from 1 to 3;
- T at each occurrence is independently a covalent bond, a carbonyl, an oxygen, -S(O)_o- or -N(R_e) R_f -;
- o is an integer from 0 to 2;
- R_e is a lone pair of electrons, a hydrogen or an alkyl group;
- R_f is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, -CH₂-C(T-Q)(R_e)(R_f), or -(N₂O₂)⁻•M⁺, wherein M⁺ is an organic or inorganic cation; with the proviso that when R_e is -CH₂-C(T-Q)(R_e)(R_f) or -(N₂O₂)⁻•M⁺, or R_e or R_f are T-Q or $(C(R_e)(R_f))_k$ -T-Q, then the "-T-Q" subgroup designated in X can be a hydrogen, an alkyl, an alkoxy, an alkoxyalkyl, an aminoalkyl, a hydroxy, a heterocyclic ring or an aryl group;

wherein the compound of formula (II) is:

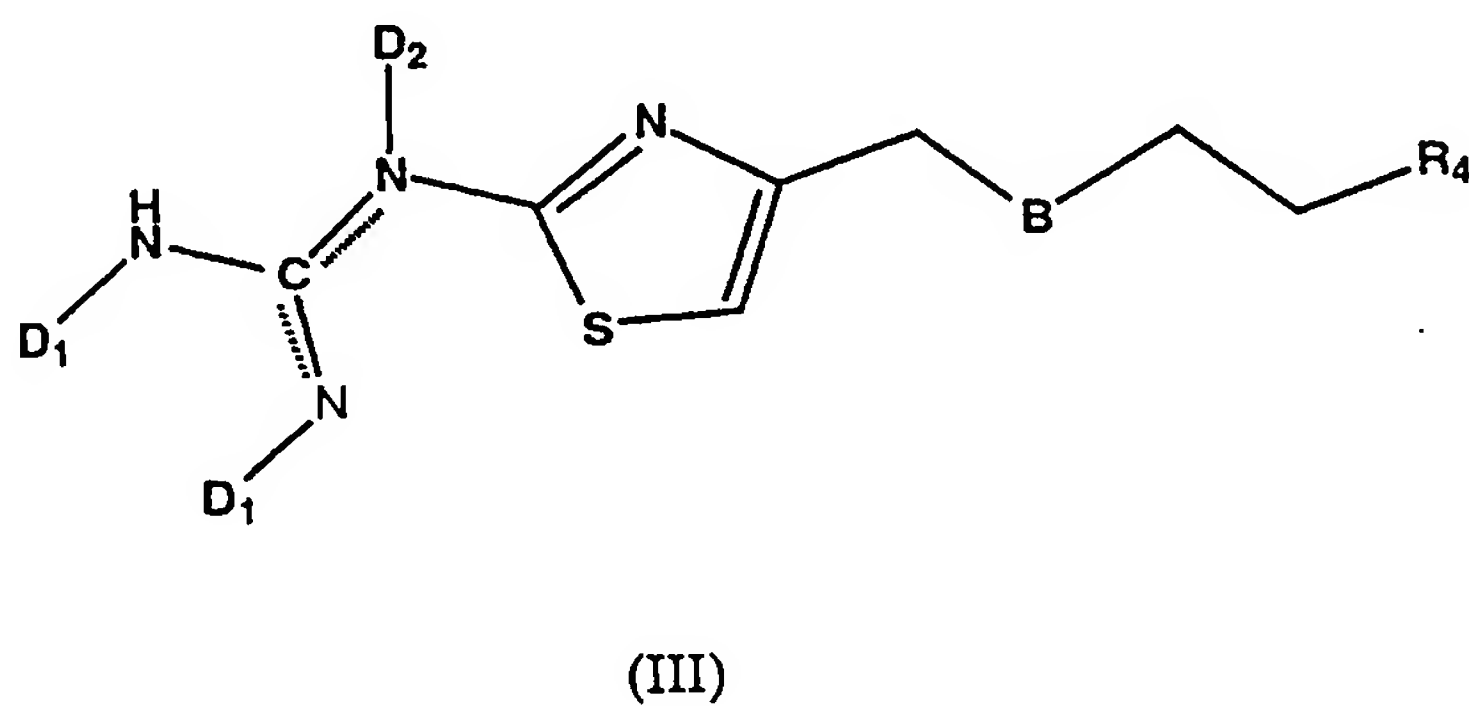


5 wherein

R_6 is a hydrogen atom, a hydroxy group or a hydroxyalkyl group; and

q , B and D are as defined herein;

wherein the compound of formula (III) is:

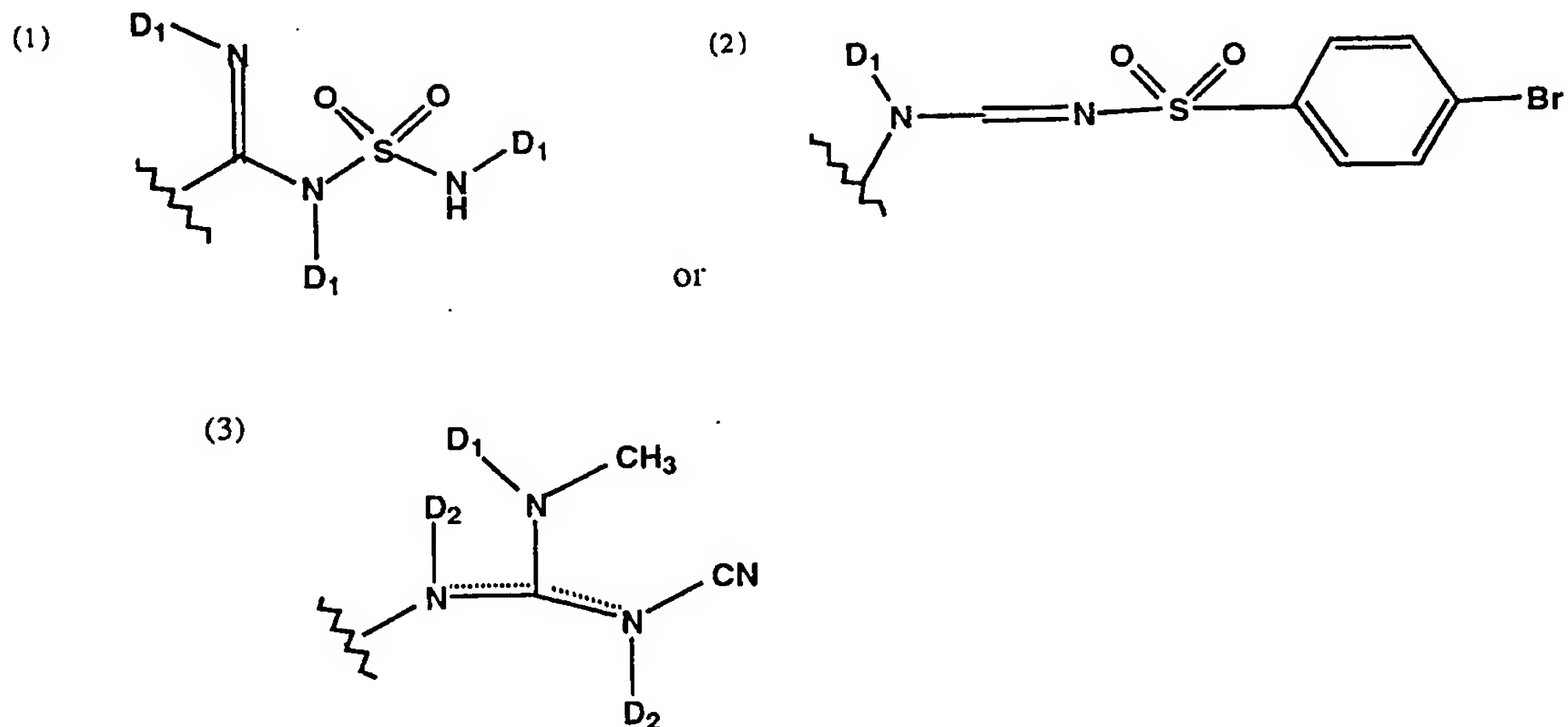


10

wherein

D_2 is D_1 or a lone pair of electrons;

R_4 is:



B, D and D_1 are as defined herein, with the proviso that at least one D_1 must be D, and D is as defined herein.

5 2. The compound of claim 1, wherein the compound of formula (I) is a nitrosated and/or nitrosylated cimetidine, a nitrosated and/or nitrosylated nizatidine, a nitrosated and/or nitrosylated rantidine, a nitrosated and/or nitrosylated burimamide or a pharmaceutically acceptable salt thereof.

10 3. The compound of claim 1, wherein the compound of formula (II) is a nitrosated and/or nitrosylated roxatidine or a pharmaceutically acceptable salt thereof.

15 4. The compound of claim 1, wherein the compound of formula (III) is a nitrosated and/or nitrosylated famotidine, a nitrosated and/or nitrosylated ebrotidine, a nitrosated and/or nitrosylated tiotidine or a pharmaceutically acceptable salt thereof.

 5. A composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

20 6. The composition of claim 5, further comprising a nonsteroidal antiinflammatory drug, an antacid, a bismuth-containing reagent or an anti-viral agent.

7. A method for treating or preventing a gastrointestinal disorder, facilitating ulcer healing, or decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 5.

5 8. The method of claim 7, further comprising administering to the patient a therapeutically effective amount of an antacid.

9. The method of claim 7, wherein the gastrointestinal disorder is a peptic ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a stress ulcer, a bleeding peptic ulcer,
10 short bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

10. A method for treating an inflammation or a microbial infection in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 5.

15 11. The method of claim 10, wherein the inflammation or microbial infection is in the eye, ear or nose of the patient or on the skin of the patient.

12. A method for treating or preventing an ophthalmic disease or disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 5.

20 13. A method of claim 12, wherein the ophthalmic disease or disorder is glaucoma, inflammation of the eye or elevation of intraocular pressure.

14. A method for treating multiple sclerosis in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 5.

25 15. A method for treating a viral infection in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 5.

16. The method of claim 15, further comprising administering to the patient a therapeutically effective amount of an anti-viral agent.

30 17. The method of claim 15, wherein the viral infection is HIV disease.

18. A method for improving the gastroprotective properties, the anti-*Helicobacter* properties, or the antacid properties of an H₂ receptor antagonist comprising administering to a patient in need thereof a therapeutically effective

amount of the pharmaceutical composition of claim 5.

19. The method of claim 18, further comprising administering to the patient a therapeutically effective amount of a bismuth-containing reagent.

20. A composition comprising at least one compound of claim 1 or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

21. The composition of claim 20 further comprising a pharmaceutically acceptable carrier.

22. The composition of claim 20, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is an S-nitrosothiol.

23. The composition of claim 22, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione.

24. The composition of claim 22, wherein the S-nitrosothiol is:

- (i) $\text{HS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{SNO}$;
 - (ii) $\text{ONS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{R}_e$; and
 - (iii) $\text{H}_2\text{N}-\text{CH}(\text{CO}_2\text{H})-(\text{CH}_2)_m-\text{C}(\text{O})\text{NH}-\text{CH}(\text{CH}_2\text{SNO})-\text{C}(\text{O})\text{NH}-\text{CH}_2-\text{CO}_2\text{H}$;
- wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an alkoxy, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkyl carboxamido, an aryl carboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a carbamoyl, a urea, a nitro, -T-Q, or $(\text{C}(\text{R}_e)(\text{R}_f))_k-\text{T-Q}$, or R_e and R_f

taken together are a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or -NO₂; and T is independently a covalent bond, a carbonyl, an oxygen, -S(O)_o- or -N(R_k)R_l-, wherein o is an integer from 0 to 2; k is an integer from 1 to 3; R_k is a lone pair of electrons, a hydrogen or an alkyl group; R_l is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, -CH₂-C(T-Q)(R_k)(R_l), or -(N₂O₂)⁻•M⁺, wherein M⁺ is an organic or inorganic cation; with the proviso that when R_l is -CH₂-C(T-Q)(R_k)(R_l) or -(N₂O₂)⁻•M⁺; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

25. The composition of claim 20, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase, is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, citrulline, ornithine or glutamine.

26. The composition of claim 20, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is:

- (i) a compound that comprises at least one ON-O-, ON-N- or ON-C- group;
- (ii) a compound that comprises at least one O₂N-O-, O₂N-N-, O₂N-S- or -O₂N-C- group;
- (iii) a N-oxo-N-nitrosoamine having the formula: R¹R²-N(O-M⁺)-NO, wherein R¹ and R² are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M⁺ is an organic or inorganic cation; or
- (iv) a thionitrate having the formula: R¹-(S)-NO₂, wherein R¹ is a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched,

saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group.

27. The composition of claim 26, wherein the compound comprising at least one ON-O-, ON-N- or ON-C- group is an ON-O-polypeptide, an ON-N-polypeptide, an ON-C-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-C-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-C-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, an ON-C-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-C-hydrocarbon, an ON-O-heterocyclic compound, an ON-N-heterocyclic compound or a ON-C-heterocyclic compound.

28. The composition of claim 26, wherein compound comprising at least one O_2N -O-, O_2N -N-, O_2N -S- or O_2N -C- group is an O_2N -O-polypeptide, an O_2N -N-polypeptide, an O_2N -S-polypeptide, an O_2N -C-polypeptide, an O_2N -O-amino acid, O_2N -N-amino acid, O_2N -S-amino acid, an O_2N -C-amino acid, an O_2N -O-sugar, an O_2N -N-sugar, O_2N -S-sugar, an O_2N -C-sugar, an O_2N -O-oligonucleotide, an O_2N -N-oligonucleotide, an O_2N -S-oligonucleotide, an O_2N -C-oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N -O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N -N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N -S-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N -C-hydrocarbon, an O_2N -O-heterocyclic compound, an O_2N -N-heterocyclic compound, an O_2N -S-heterocyclic compound or an O_2N -C-heterocyclic compound.

29. The composition of claim 20, further comprising a nonsteroidal antiinflammatory drug, an antacid, a bismuth-containing reagent or an anti-viral agent.

30. A method for treating or preventing a gastrointestinal disorder, facilitating ulcer healing, or decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective

amount of the composition of claim 20.

31. The method of claim 30, further comprising administering to the patient a therapeutically effective amount of an antacid.

5 32. The method of claim 30, wherein the gastrointestinal disorder is a peptic ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a stress ulcer, a bleeding peptic ulcer, short bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

10 33. A method for treating an inflammation or a microbial infection in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 20.

34. The method of claim 33, wherein the inflammation or microbial infection is in the eye, ear or nose of the patient or on the skin of the patient.

15 35. A method for treating or preventing an ophthalmic disease or disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 20.

36. A method of claim 35, wherein the ophthalmic disease or disorder is glaucoma, inflammation of the eye or elevation of intraocular pressure.

20 37. A method for treating multiple sclerosis in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 20.

38. A method for treating a viral infection in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 20.

25 39. The method of claim 38, further comprising administering to the patient a therapeutically effective amount of an anti-viral agent.

40. The method of claim 38, wherein the viral infection is HIV disease.

30 41. A method for improving the gastroprotective properties, the anti-*Helicobacter* properties, or the antacid properties of an H₂ receptor antagonist comprising administering to a patient in need thereof a therapeutically effective amount of the composition of claim 20.

42. The method of claim 41, further comprising administering to the patient a therapeutically effective amount of a bismuth-containing reagent.

43. A composition comprising at least one H_2 receptor antagonist compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

44. The composition of claim 43, wherein the at least one H_2 receptor antagonist compound is cimetidine, nizatidine, rantidine, roxatidine, famotidine, ebrotidine, burimamide, metiamide, tiotidine or oxmetidine.

45. The composition of claim 43 further comprising a pharmaceutically acceptable carrier.

46. The composition of claim 43, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is an S-nitrosothiol.

47. The composition of claim 46, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione.

48. The composition of claim 46, wherein the S-nitrosothiol is:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; and

(iii) $H_2N-CH(CO_2H)-(CH_2)_m-C(O)NH-CH(CH_2SNO)-C(O)NH-CH_2-CO_2H$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylaryl amino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an alkoxy, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkyl carboxamido, an aryl carboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a carbamoyl, a urea, a nitro, -T-Q, or $(C(R_e)(R_f))_k-T-Q$, or R_e and R_f

taken together are a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or -NO₂; and T is independently a covalent bond, a carbonyl, an oxygen, -S(O)_o- or -N(R_k)R_l-, wherein o is an integer from 0 to 2; k is an integer from 1 to 3; R_k is a lone pair of electrons, a hydrogen or an alkyl group; R_l is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, -CH₂-C(T-Q)(R_e)(R_f), or -(N₂O₂-)•M⁺, wherein M⁺ is an organic or inorganic cation; with the proviso that when R_l is -CH₂-C(T-Q)(R_e)(R_f) or -(N₂O₂-)•M⁺; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

49. The composition of claim 43, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, citrulline, ornithine or glutamine.

50. The composition of claim 43, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is:

- (i) a compound that comprises at least one ON-O-, ON-N- or ON-C-group;
- (ii) a compound that comprises at least one O₂N-O-, O₂N-N-, O₂N-S- or -O₂N-C- group;
- (iii) a N-oxo-N-nitrosoamine having the formula: R¹R²-N(O-M⁺)-NO, wherein R¹ and R² are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M⁺ is an organic or inorganic cation; or
- (iv) a thionitrate having the formula: R¹-(S)-NO₂, wherein R¹ is a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched,

saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group.

51. The composition of claim 50, wherein the compound comprising at least one ON-O-, ON-N- or ON-C- group is an ON-O-polypeptide, an ON-N-polypeptide, an ON-C-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-C-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-C-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, an ON-C-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-C-hydrocarbon, an ON-O-heterocyclic compound, an ON-N-heterocyclic compound or a ON-C-heterocyclic compound.

52. The composition of claim 50, wherein compound comprising at least one O_2N -O-, O_2N -N-, O_2N -S- or O_2N -C- group is an O_2N -O-polypeptide, an O_2N -N-polypeptide, an O_2N -S-polypeptide, an O_2N -C-polypeptide, an O_2N -O-amino acid, O_2N -N-amino acid, O_2N -S-amino acid, an O_2N -C-amino acid, an O_2N -O-sugar, an O_2N -N-sugar, O_2N -S-sugar, an O_2N -C-sugar, an O_2N -O-oligonucleotide, an O_2N -N-oligonucleotide, an O_2N -S-oligonucleotide, an O_2N -C-oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N -O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N -N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N -S-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N -C-hydrocarbon, an O_2N -O-heterocyclic compound, an O_2N -N-heterocyclic compound, an O_2N -S-heterocyclic compound or an O_2N -C-heterocyclic compound.

53. The composition of claim 43, further comprising a nonsteroidal antiinflammatory drug, an antacid, a bismuth-containing reagent or an anti-viral agent.

54. A method for treating or preventing a gastrointestinal disorder, facilitating ulcer healing, or decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective

amount of the composition of claim 43.

55. The method of claim 54, further comprising administering to the patient a therapeutically effective amount of an antacid.

56. The method of claim 54, wherein the gastrointestinal disorder is a
5 peptic ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison
syndrome, gastroesophageal reflux disease, a stress ulcer, a bleeding peptic ulcer,
short bowel syndrome, or a hypersecretory state associated with systemic
mastocytosis or basophilic leukemia and hyperhistaminemia.

57. A method for treating an inflammation or a microbial infection in a
10 patient in need thereof comprising administering to the patient a therapeutically
effective amount of the composition of claim 43.

58. The method of claim 57, wherein the inflammation or microbial
infection is in the eye, ear or nose of the patient or on the skin of the patient.

59. A method for treating or preventing an ophthalmic disease or
15 disorder in a patient in need thereof comprising administering to the patient a
therapeutically effective amount of the pharmaceutical composition of claim 43.

60. A method of claim 59, wherein the ophthalmic disease or disorder is
glaucoma, inflammation of the eye or elevation of intraocular pressure.

61. A method for treating multiple sclerosis in a patient in need thereof
20 comprising administering to the patient a therapeutically effective amount of the
composition of claim 43.

62. A method for treating a viral infection in a patient in need thereof
comprising administering to the patient a therapeutically effective amount of the
composition of claim 43.

25 63. The method of claim 62, further comprising administering to the
patient a therapeutically effective amount of an anti-viral agent.

64. The method of claim 62, wherein the viral infection is HIV disease.

65. A method for improving the gastroprotective properties, the anti-
Helicobacter properties, or the antacid properties of an H₂ receptor antagonist
30 comprising administering to a patient in need thereof a therapeutically effective
amount of the composition of claim 43.

66. The method of claim 65, further comprising administering to the
patient a therapeutically effective amount of a bismuth-containing reagent.

67. A method for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroid antiinflammatory drug to a patient comprising administering to a patient in need thereof a therapeutically effective amount of at least one nonsteroidal antiinflammatory drug and at least one composition of claim 5.

68. A method for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroid antiinflammatory drug to a patient comprising administering to a patient in need thereof a therapeutically effective amount of at least one nonsteroidal antiinflammatory drug and at least one composition of claim 21.

69. A method for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroid antiinflammatory drug to a patient comprising administering to a patient in need thereof a therapeutically effective amount of at least one nonsteroidal antiinflammatory drug, at least one compound of claim 5, and at least one composition that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

70. A method for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroid antiinflammatory drug to a patient comprising administering to a patient in need thereof a therapeutically effective amount of at least one nonsteroidal antiinflammatory drug and at least one composition of claim 45.

71. A method for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroid antiinflammatory drug to a patient comprising administering to a patient in need thereof a therapeutically effective amount of at least one nonsteroidal antiinflammatory drug, at least one H_2 receptor antagonist compound, and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

72. A method for improving the gastroprotective properties, the anti-*Helicobacter* properties or the antacid properties of an H_2 receptor antagonist

compound comprising administering to a patient in need thereof a therapeutically effective amount of a bismuth complex comprising at least one composition of claim 5.

5 73. A method for improving the gastroprotective properties, the anti-*Helicobacter* properties or the antacid properties of an H₂ receptor antagonist compound comprising administering to a patient in need thereof a therapeutically effective amount of a bismuth complex comprising at least one composition of claim 21.

10 74. A method for improving the gastroprotective properties, the anti-*Helicobacter* properties or the antacid properties of an H₂ receptor antagonist compound comprising administering to a patient in need thereof a therapeutically effective amount of a bismuth complex comprising at least one composition of claim 45.

15 75. A method for preventing or treating a gastrointestinal disorder, facilitating ulcer healing, or decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the compound of claim 1 or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing
20 factor, or is a substrate for nitric oxide synthase.

76. The method of claim 75, further comprising administering at least one antacid.

25 77. The method of claim 75, wherein the gastrointestinal disorder is a peptic ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a stress ulcer, a bleeding peptic ulcer, short bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

30 78. A method for preventing or treating a gastrointestinal disorder, facilitating ulcer healing, or decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one H₂ receptor antagonist or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived

relaxing factor, or is a substrate for nitric oxide synthase.

79. The method of claim 78, further comprising administering at least one antacid.

80. The method of claim 78, wherein the gastrointestinal disorder is a
5 peptic ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a stress ulcer, a bleeding peptic ulcer, short bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

81. A method for treating an inflammation or a microbial infection in a
10 patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one composition of claim 5 and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

15 82. The method of claim 81, wherein the inflammation or microbial infection is in the eye, ear or nose of the patient or on the skin of the patient.

83. A method for treating an inflammation or a microbial infection in a
patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one H_2 receptor antagonist compound or a
20 pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

84. The method of claim 83, wherein the inflammation or microbial
25 infection is in the eye, ear or nose of the patient or on the skin of the patient.

85. A method for treating or preventing an ophthalmic disease or
disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one composition of claim 5 and at least
one compound that donates, transfers or releases nitric oxide, or induces the
30 production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

86. A method of claim 85, wherein the ophthalmic disease or disorder is
glaucoma, inflammation of the eye or elevation of intraocular pressure.

87. A method for treating multiple sclerosis in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one compound of claim 5 and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

88. A method for treating multiple sclerosis in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one H_2 receptor antagonist compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

89. A method for treating a viral infection in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one composition of claim 5, and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

90. The method of claim 89, further comprising administering to the patient a therapeutically effective amount of an anti-viral agent.

91. The method of claim 89, wherein the viral infection is HIV disease.

92. A method for treating a viral infection in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one H_2 receptor antagonist compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

93. The method of claim 92, further comprising administering to the patient a therapeutically effective amount of an anti-viral agent.

94. The method of claim 92, wherein the viral infection is HIV disease.

95. A kit comprising at least one compound of claim 1 or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

96. The kit of claim 95, wherein the compound of claim 1 or the pharmaceutically acceptable salt thereof, and the compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase are separate components in the kit or are in the form of a composition in the kit.

97. The kit of claim 95, further comprising a nonsteroidal antiinflammatory drug, an antacid, a bismuth-containing reagent or an anti-viral agent.

98. A kit comprising at least one H_2 receptor antagonist compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

99. The kit of claim 98, wherein the H_2 receptor antagonist compound or the pharmaceutically acceptable salt thereof, and the compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase are separate components in the kit or are in the form of a composition in the kit.

100. The kit of claim 98, further comprising a nonsteroidal antiinflammatory drug, an antacid, a bismuth-containing reagent or an anti-viral agent.

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Figure 1

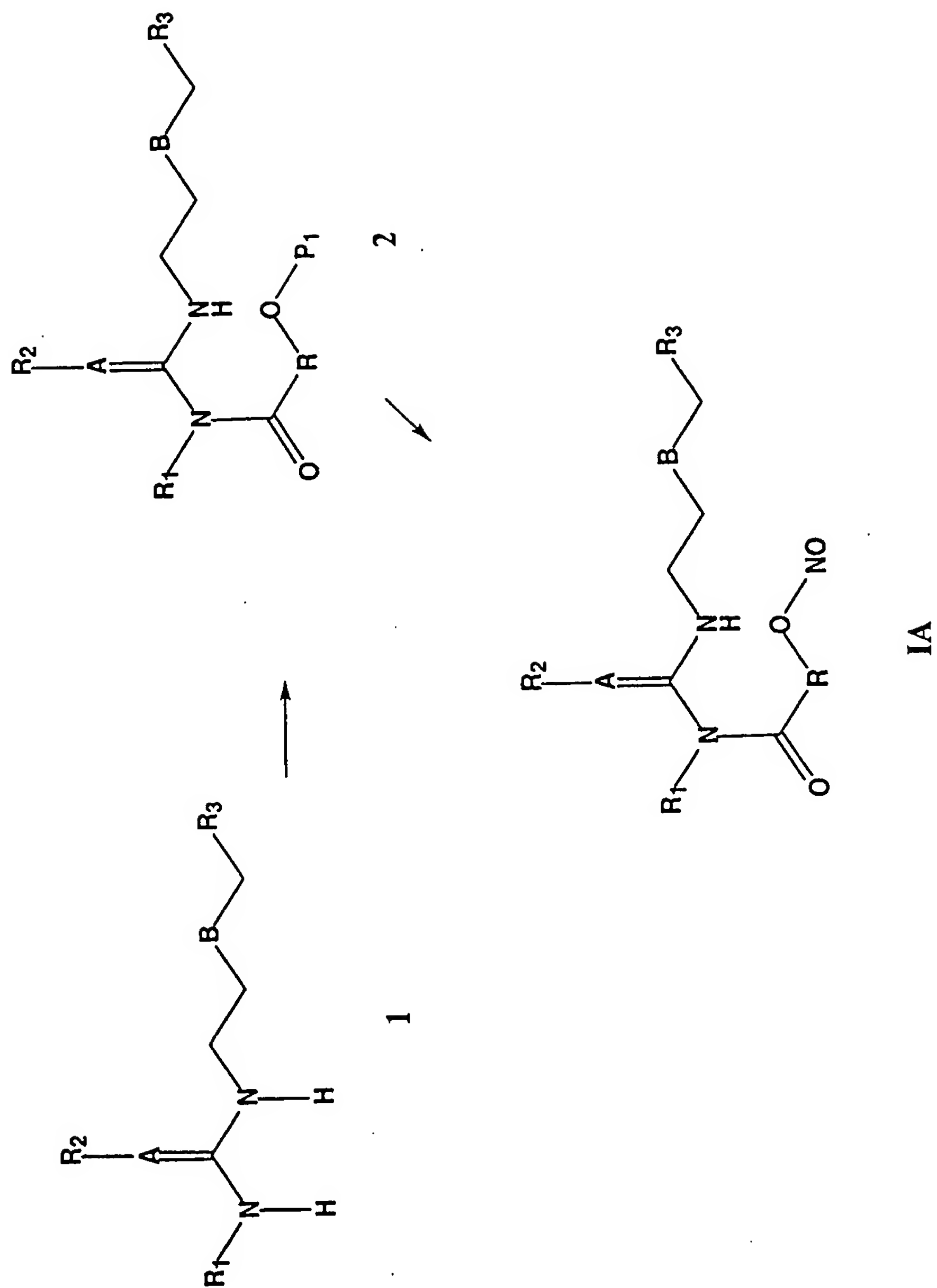


Figure 2

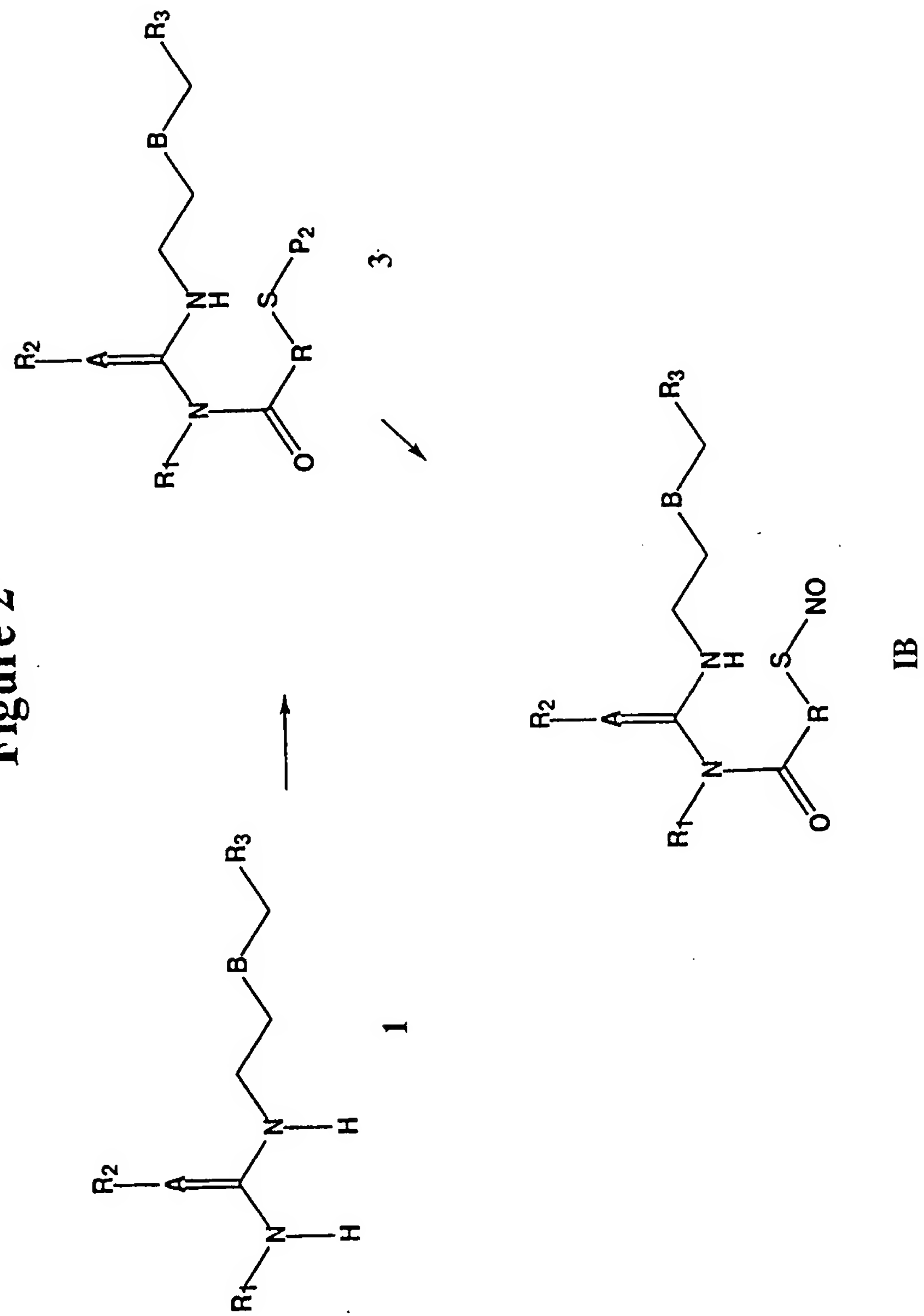


Figure 3

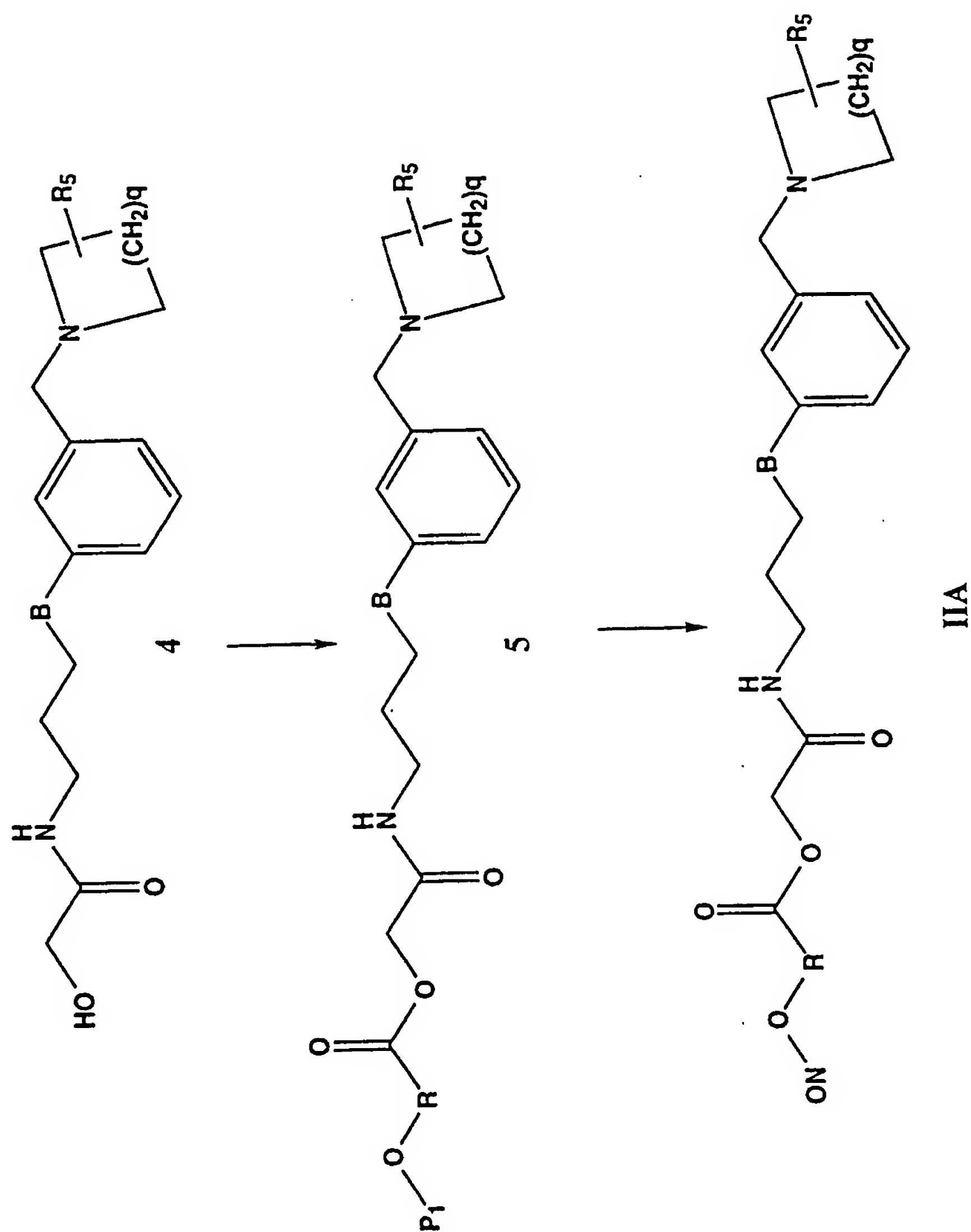


Figure 5

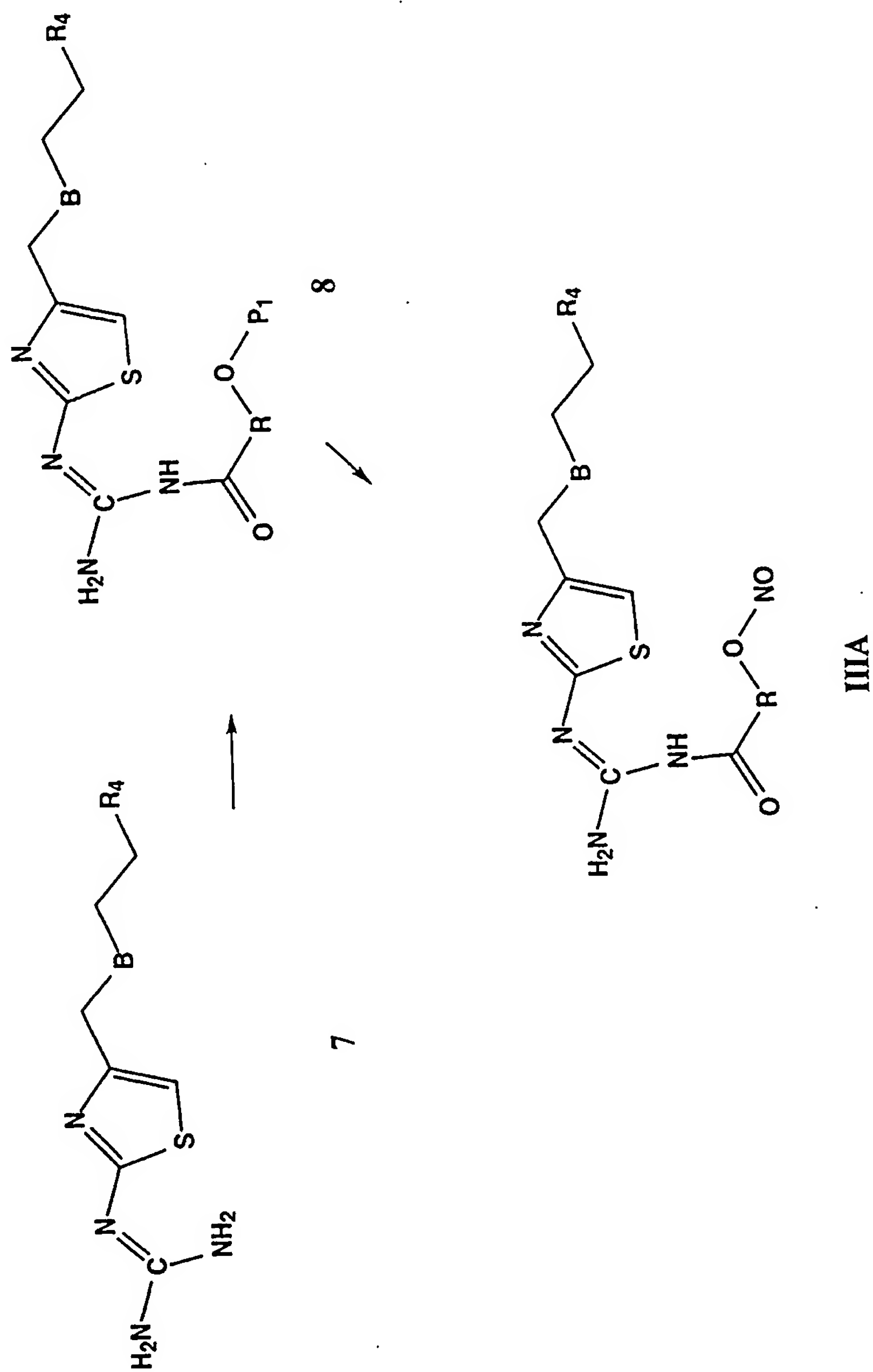


Figure 6

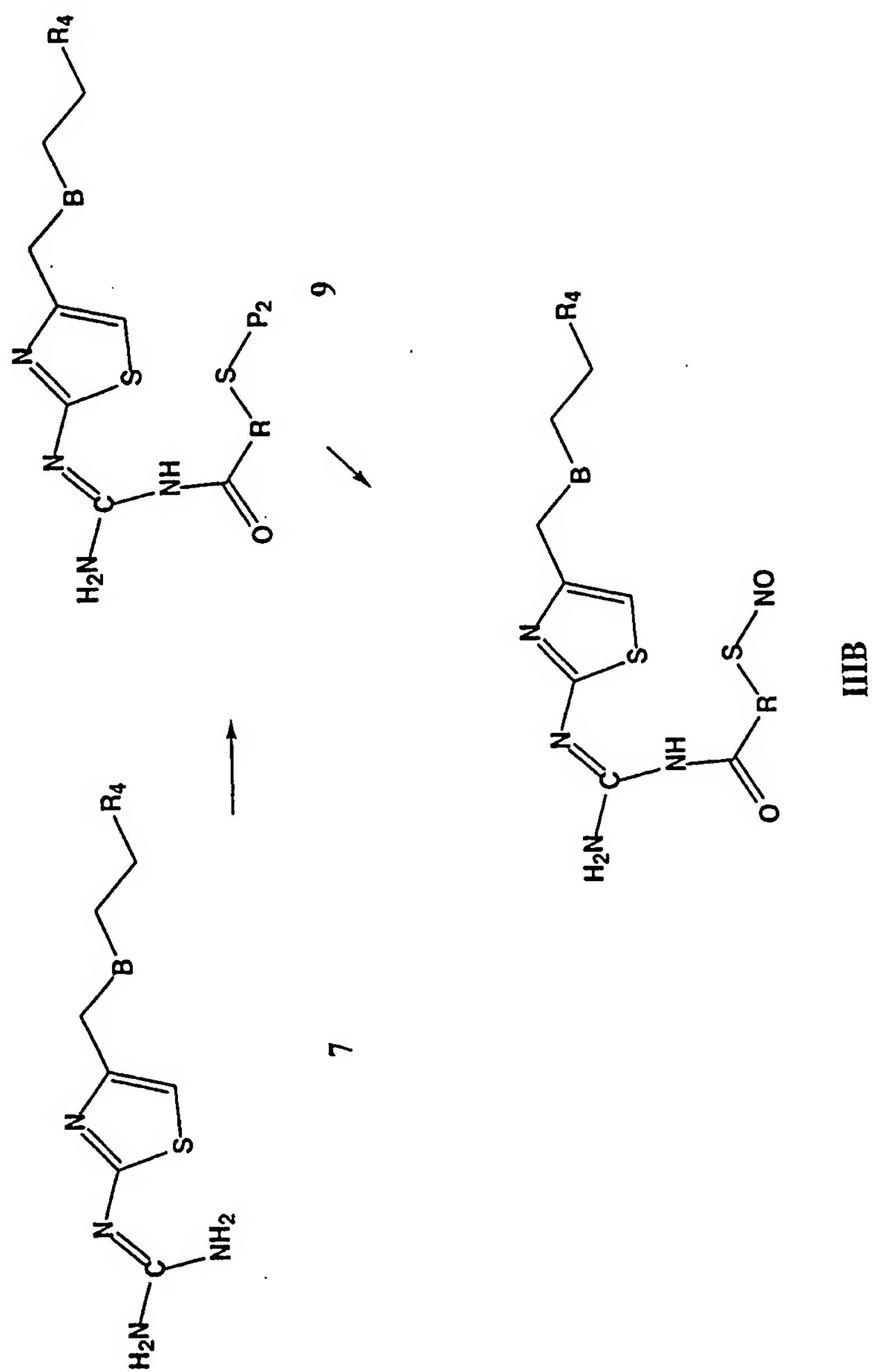
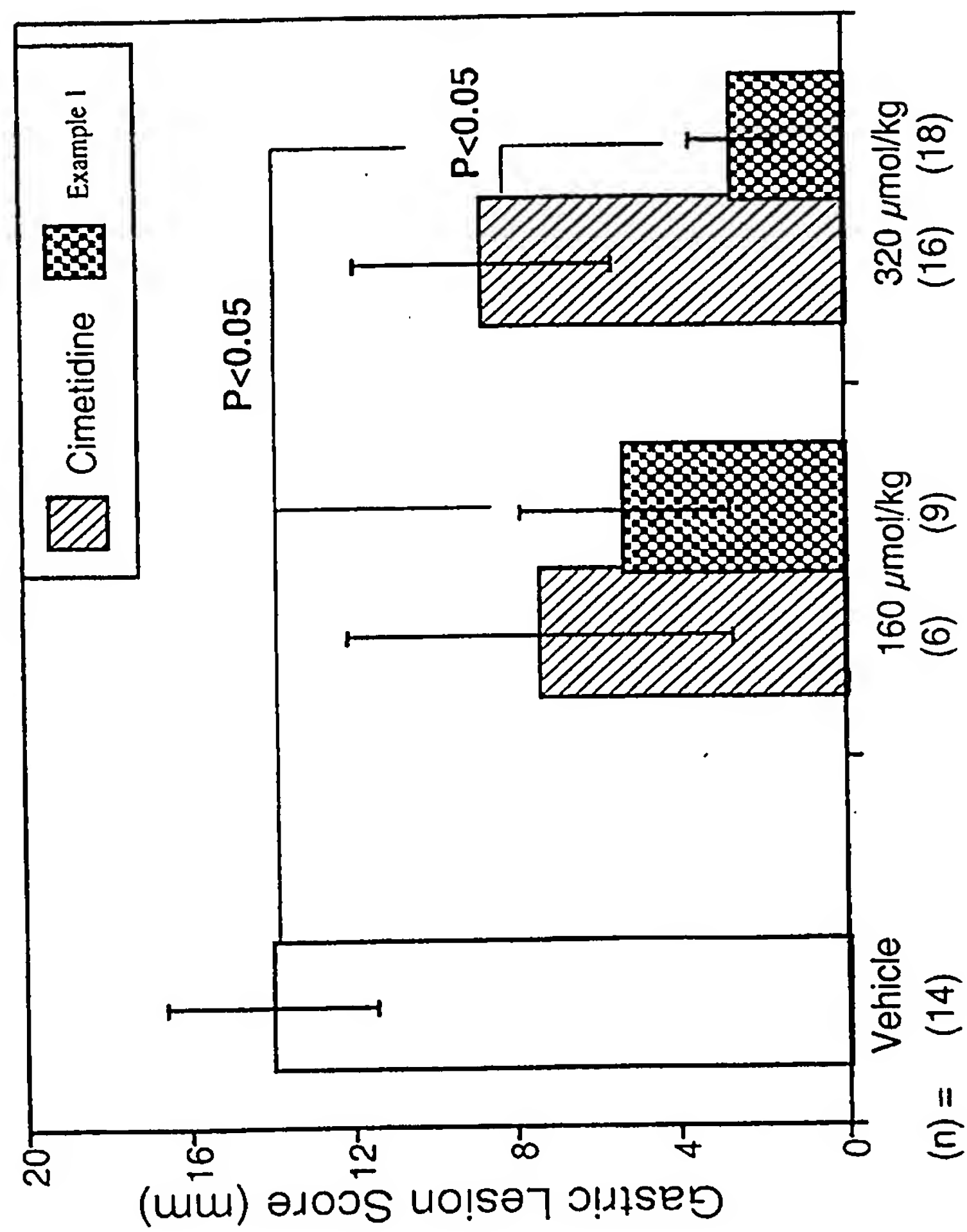


Figure 7



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/27207

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/331, 365, 370, 400, 471; 546/233; 548/197, 205, 561; 549/495

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FRANEKIC et al. Genotoxicity of Ranitidine. Mutation Research. 1989, Vol. 227, pages 13-16, see entire document.	1, 2
X	HASSAN et al. Determination of Ranitidine in Pharmaceutical Preparations using Manual and Flow Injection Potentiometry and Spectrophotometry. Analytica Chimica Acta. 1996, Vol. 332, pages 39-48, see entire document.	1, 2



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search

21 MARCH 2000

Date of mailing of the international search report

04 APR 2000

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Authorized officer

ROBERT GERSTL - 

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/27207

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

A61K 31/341, 31/4164, 31/417, 31/427, 31/4453; C07D 211/06, 233/64, 277/28, 277/48, 277/52, 307/52

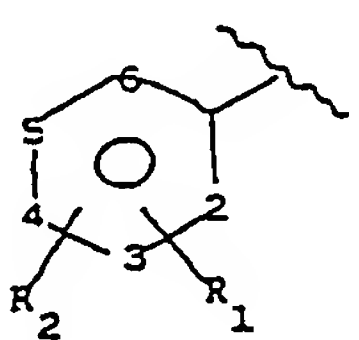
A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/331, 365, 370, 400, 471; 546/233; 548/197, 205, 561; 549/495

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 213/30, 401/12, A61K 31/44, A61P 29/00, 7/02		A1	(11) International Publication Number: WO 00/51988
			(43) International Publication Date: 8 September 2000 (08.09.00)
(21) International Application Number: PCT/EP00/01454 (22) International Filing Date: 23 February 2000 (23.02.00) (30) Priority Data: MI99A000413 2 March 1999 (02.03.99) IT (71) Applicant (for all designated States except US): NICOX S.A. [FR/FR]; 45, Avenue Kléber, F-75116 Paris (FR). (72) Inventors; and (75) Inventors/Applicants (for US only): BENEDINI, Francesca [IT/IT]; Via Padova, 286, I-20100 Milano (IT). DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I-20052 Monza (IT). (74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni, 2, I-20129 Milano (IT).		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: NITROXYDERIVATIVES HAVING ANTIINFLAMMATORY, ANALGESIC AND ANTITHROMBOTIC ACTIVITY			
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>(Ia)</p> </div> <div style="text-align: center;"> $\begin{array}{c} R_{TIX} \\ \\ -(C)_{nIX} - Y - (C)_{nIIX} - O - \\ \\ R_{TIX'} \end{array}$ <p>(B)</p> </div> </div>			
(57) Abstract Organic or inorganic salts of compounds of general formula: A - X ₁ - N(O) ₂ for use as medicaments having anti-inflammatory, analgesic and antithrombotic activity, wherein A is R(COX _u) _t wherein t is 0 or 1; u is 0 or 1 and X is O, NH, NR _{1c} wherein R _{1c} is a C ₁ -C ₁₀ alkyl and R is, for example, (Ia) wherein R ₁ is acetoxy, preferably in ortho position with respect to -CO- and R ₂ is hydrogen or acetylsalicylsalicylic acid derivatives; and X ₁ is the formula (B), Y being a ring containing at least one salified nitrogen atom.			

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NITROXYDERIVATIVES HAVING ANTIINFLAMMATORY, ANALGESIC AND ANTITHROMBOTIC ACTIVITY

* * * * *

The present invention relates to new products having anti-inflammatory, analgesic and antithrombotic activity.

Specifically it relates to cyclo-oxygenase (COX) inhibitors.

It is known that the anti-inflammatory and antithrombotic efficacy of NSAIDs (Non steroid antiinflammatory drugs), also known as FANS (non steroid antiinflammatory drugs), but especially their tolerability, seem to be considerably affected by their inhibitory activity of the cyclo-oxygenase (COX) both in the inflammatory site and in the healthy tissue. See for example FASEB Journal 1, 89, 1987; Bioch. Biophys. Acta 1083, 1, 1991. The drawback of these products is that they are toxic, as already described in USP 5,861,426.

Nitroderivative compounds, described in said patent, are also known, have an high efficacy in the cyclooxygenase inhibition and a low toxicity. However these compounds show some drawbacks connected to the chemical-physical and structural characteristics of the molecules themselves, these latter being highly lipophilic and therefore having a poor solubility in water. It is well known that the solubilization process is decisive for absorption and interaction with the

effector. The poor solubility generally involves a variable and unpredictable efficacy whereby it is difficult to set a correct posology. In practice it is necessary to administer higher doses in order to contain the above mentioned variabilities. The drawback is the risks of a higher incidence of side effects. Another disadvantage bound to the poor solubility of the nitroderivatives of said patent application is that they are difficult to be formulated. It is well known that the solubility in water of a molecule is one of the most important properties affecting the pharmacokinetic and pharmacodynamic processes. For example for parenteral administration, particularly by intravenous route, drugs must be formulated in solutions. In order to increase solubility, when it is unsatisfactory for these uses, the choice of suitable solvents and/or excipients is therefore critical, for example, among the latter, surfactants, etc., can be mentioned. This can lead to drawbacks from the toxicological point of view connected to the excipient tolerability; besides there are other drawbacks for example in the intravenous formulation which, as well known, must not cause haemolysis or incompatibility with blood constituents. Besides it is necessary to notice that it is well known that surfactants and apolar solvents can be irritant. See for example J. Pharm. Science 72, 1014, 1983.

Experiments carried out by the Applicant, wherein 0.1%

Tween 80 and 1% dimethylsulphoxide have been used to suspend the nitroxy derivatives of the antiinflammatory compounds described in the patent application WO 95/30641 have shown that these substances were irritant towards the gastric mucous membrane.

It has unexpectedly been found that the derivatives of the present invention, differently from the above mentioned compounds of the prior art, can be solubilized without using the substances commonly used in the pharmaceutical technique to obtain solutions or suspensions, maintaining or even improving the activity of the prior art nitroxy derivatives. A further advantage of the compounds of the present invention is that it is possible to avoid adding to the formulation the excipients, such as for example those above mentioned, which cause or can induce irritant effects.

The antiinflammatory products described in the present application have an high cyclo-oxygenase inhibiting activity combined with low toxicity and pharmacokinetic good responses, and have furthermore a better systemic absorption degree.

This is quite surprising and unexpected since the factors affecting the FANS antiinflammatory and antithrombotic efficacy depend on various parameters whereby it is not possible to foresee a priori the pharmacokinetics, for example the absorbed product fraction, the pharmacodynamic activity, the toxicity and the COX inhibiting properties and most of

all, no assumptions can be made to predict or limit the response variability.

An object of the present invention are compounds or organic or inorganic salts of compounds of general formula:

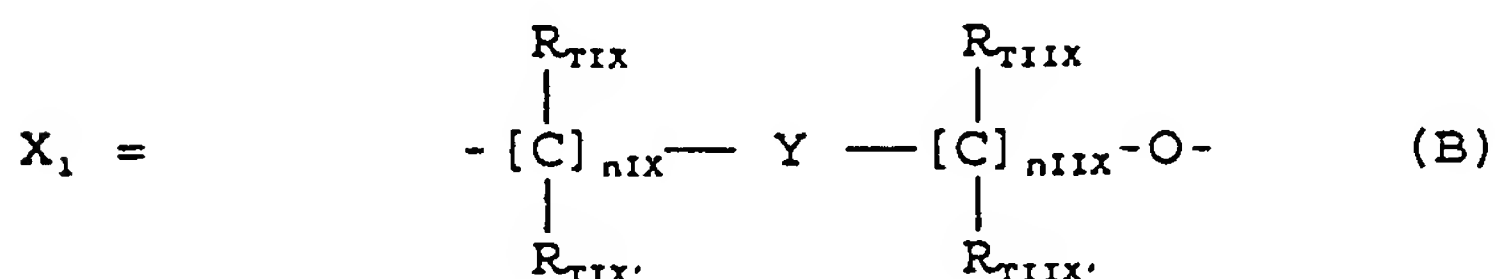


for use as medicaments, specifically as antiinflammatory and antithrombotic agents, wherein:

z is an integer and is 1 or 2, preferably 2;

A = R(COX_u)_t and wherein t is an integer 0 or 1; u is 0 or 1;

X = O, NH, NR_{1c} wherein R_{1c} is a linear or branched C₁-C₁₀ alkyl;



wherein:

nIX is an integer between 0 and 3, preferably 1;

nIIX is an integer between 1 and 3, preferably 1;

R_{TIX}, R_{TIX'}, R_{TIIIX}, R_{TIIIX'}, equal to or different from each other, are H or linear or branched C₁-C₄ alkyl; preferably R_{TIX}, R_{TIX'}, R_{TIIIX}, R_{TIIIX'} are H;

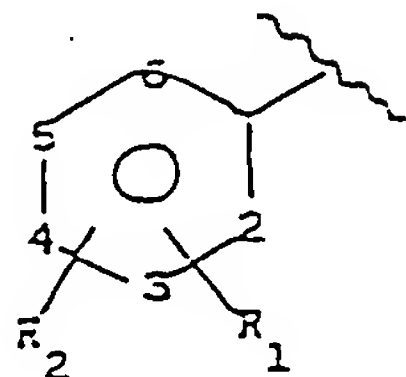
Y is a ring containing at least one salifiable nitrogen atom; preferably Y is an heterocyclic ring, saturated or unsaturated or aromatic, having preferably 5 or 6 atoms and containing at least one or two nitrogen atoms, preferably one or two

nitrogen atoms;

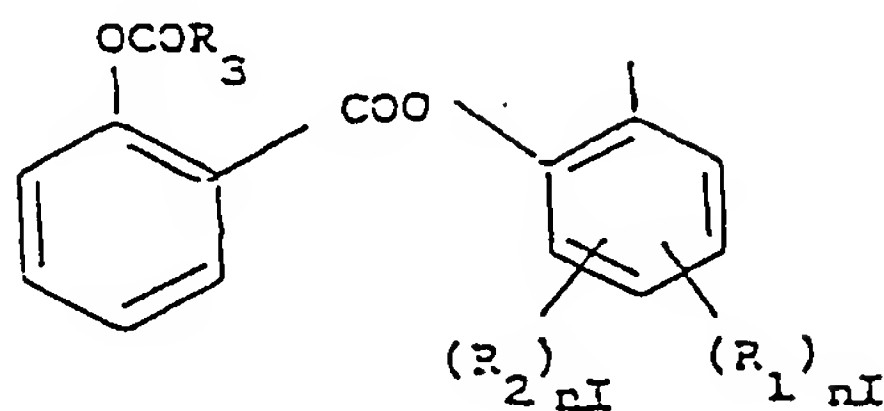
R is selected from the following groups:

Group I) wherein $t = 1$ and $u = 1$

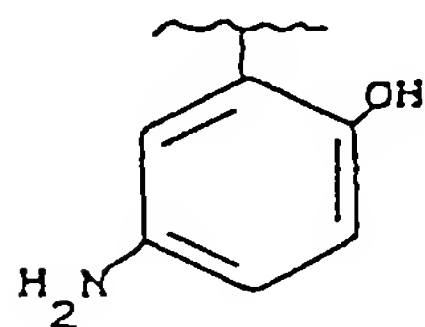
Ia)



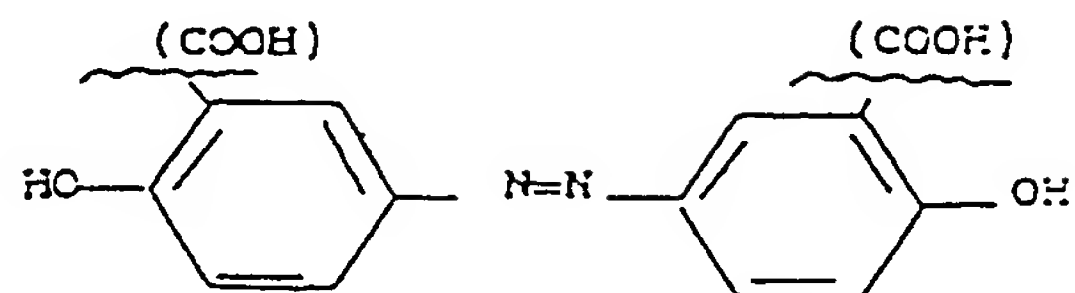
Ib)



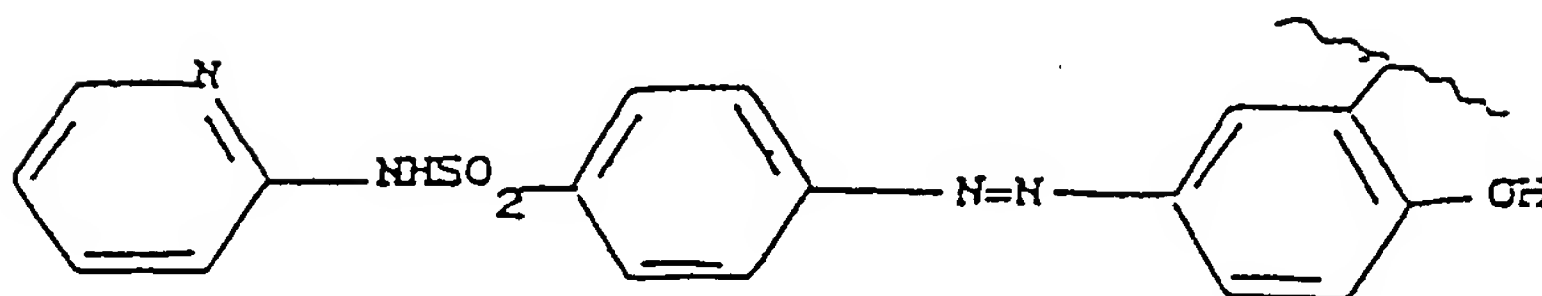
Ic)



IC₁)



IC₂)



IC₃)

wherein:

R_1 is the $OCOR_2$ group; wherein R_2 is methyl, ethyl or linear or branched C_3-C_5 alkyl, or the residue of a heterocycle with a single ring having 5 or 6 atoms which may be aromatic, partially or totally hydrogenated, containing one or more hetero-atoms independently selected from O, N and S;

R_2 is hydrogen, hydroxy, halogen, a linear or when possible branched C_1-C_4 alkyl, a linear or when possible branched C_1-C_4 alkoxyl; a linear or when possible branched C_1-C_4 perfluoroalkyl, for example trifluoromethyl; nitro, amino, mono- or di- (C_{1-4}) alkylamino;

nI is an integer 0 or 1;

preferably in the compounds of formula Ia) X is equal to O or NH, R_1 is acetoxy, preferably in ortho position with respect to $-CO-$, R_2 is hydrogen; in $X_1 R_{TIX} = R_{TIX'} = R_{TIX''} = R_{TIX'''} = H$, $n_{IX} = n_{IX'} = 1$ and Y is an aromatic ring having 6 atoms, containing one nitrogen atom, said aromatic ring having the two free valences in position 2 and 6.

Preferably in the compounds of formula Ib) $R_2 = CH_3$, $nI = 0$, X is equal to O, X_1 is as above defined for Ia); in this case Ib) is the residue of the acetylsalicylsalicylic acid.

The compounds Ic) of formula Ic₁) are the 5-amino salicylic acid derivatives (5-amino-2-hydroxybenzoic acid), for example mesalamine, when the valence is saturated with $-COOH$.

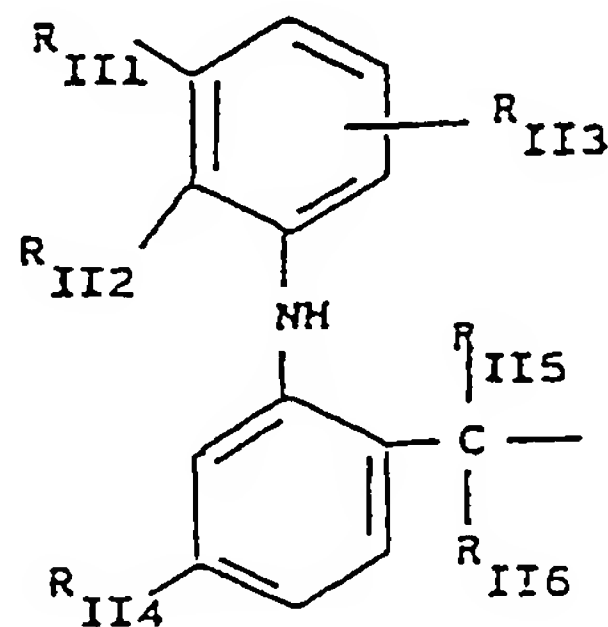
In the compounds of formula Ic₂) at least one of the two carboxyl groups is reacted for obtaining the invention compounds. When both carboxyl groups react, bifunctional compounds are obtained. When the two valences are saturated with -COOH, the compound known as olsalazine is obtained. When one of the two valences instead of -COOH is saturated with -CONHCH₂-CH₂-COOH, the compound is known as balsalazide, wherein -OH which is in ortho position in the same aromatic ring is substituted with H.

The compounds of formula IC₃) are known as sulphalazine: 2-hydroxy-5-[(2-pyridinylamino)sulphonyl]phenyl]azo] benzoic acid when the free valence is saturated with -COOH.

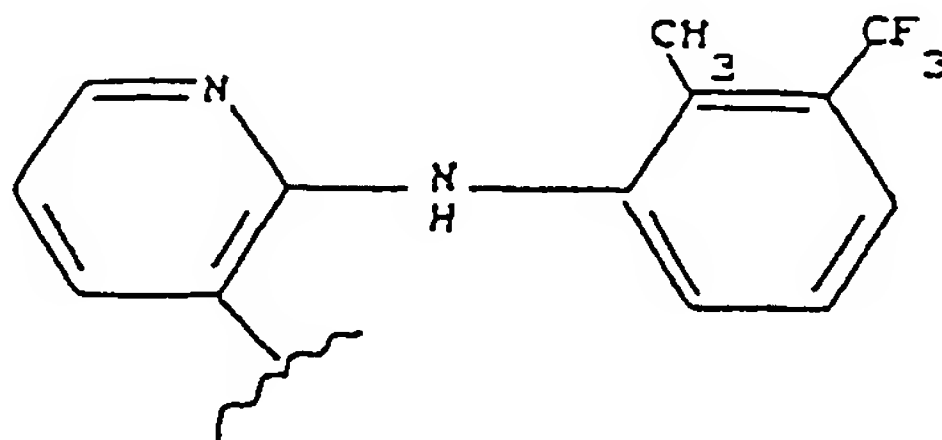
The preferred Ic) compounds have X = O and u = 1;

Group II) wherein t = 1, u = 1

IIa)



IIb)



wherein:

R_{II5} is H, a linear or branched when possible C_1 - C_6 alkyl;

R_{II6} has the same meaning as R_{II5} , or when R_{II5} is H it may be benzyl;

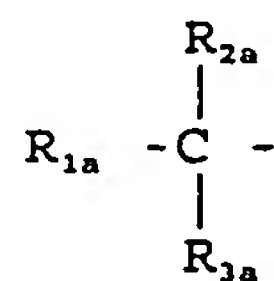
R_{III1} , R_{III2} and R_{III3} can independently be hydrogen, a linear or when possible branched C_1 - C_6 alkyl or a linear or when possible branched C_1 - C_6 alkoxy, or Cl, F, Br;

R_{II4} is R_{III1} or bromine;

the compounds wherein R_{III1} , R_{II4} are hydrogen and R_{III2} and R_{III3} are chlorine in ortho position with respect to NH are preferred; R_{II5} and R_{II6} are H, X is equal to O, and X_1 is as above defined for the compounds of formula Ia);

Iib) is the residue of the 2-[(2-methyl-3-(trifluoromethyl)phenyl)amino]-3-pyridinecarboxylic acid and when the -COOH group is present the compound is known as flunixin;

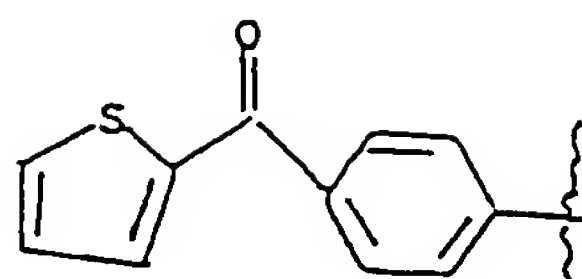
Group III) wherein $t = 1$, $u = 1$ and R is



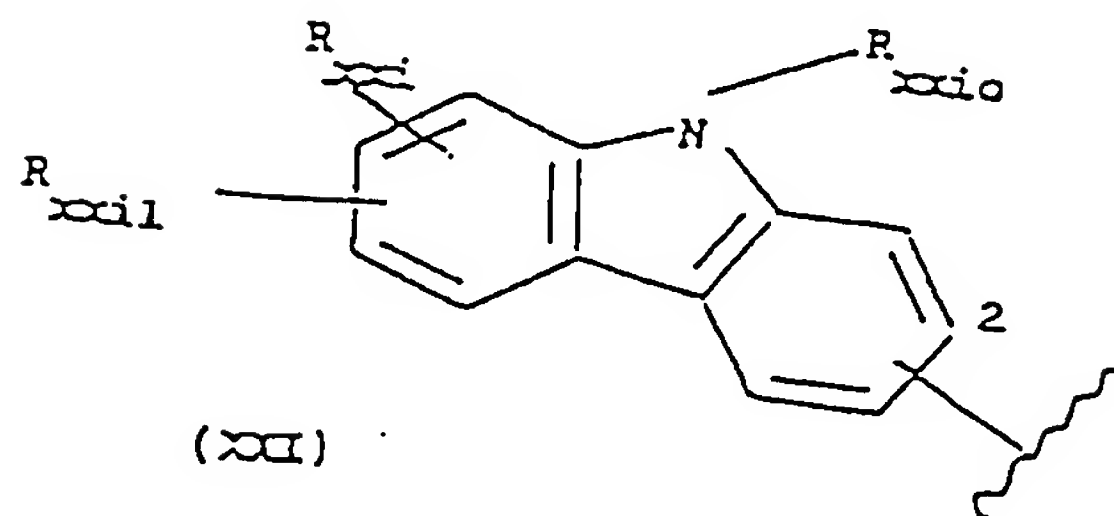
wherein:

R_{2a} and R_{3a} are H, a linear or when possible branched, substituted or non-substituted, C_1 - C_{12} alkyl or allyl, with the proviso that when one of the two is allyl, the other is H; preferably R_{2a} is H, C_1 - C_4 alkyl, R_{3a} is H;

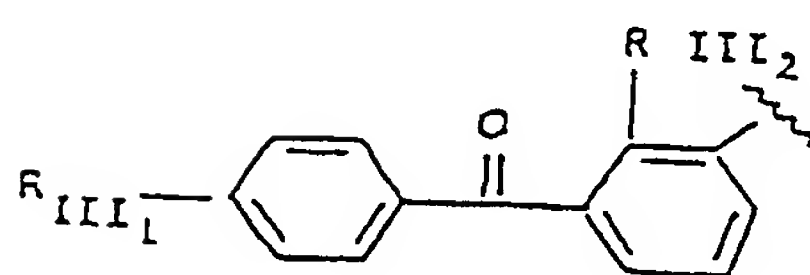
R_{1a} is selected from



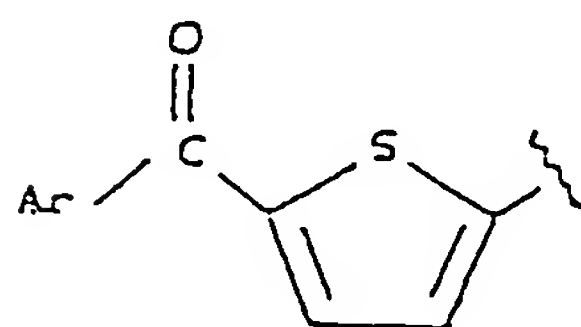
(III)



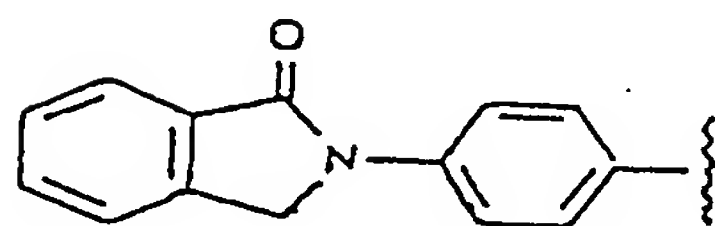
(XXI)



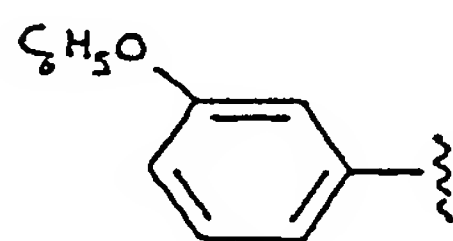
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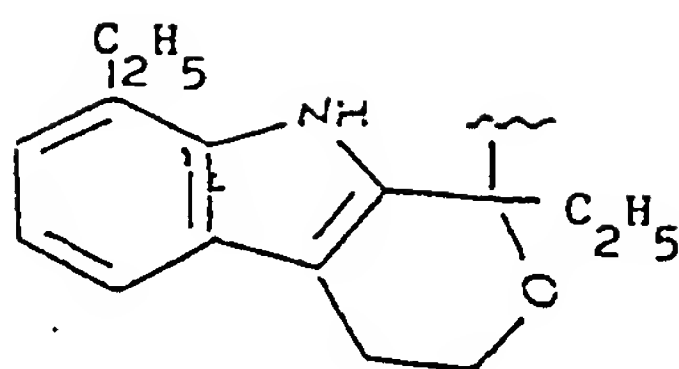
(XXXV)



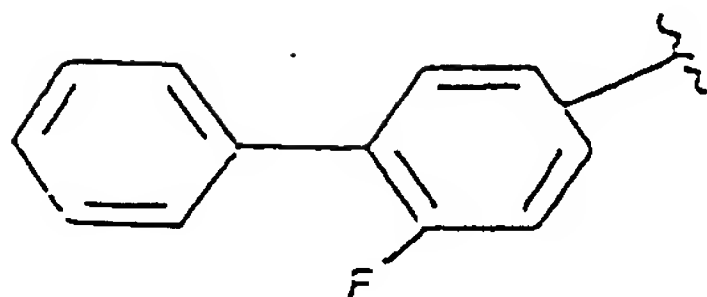
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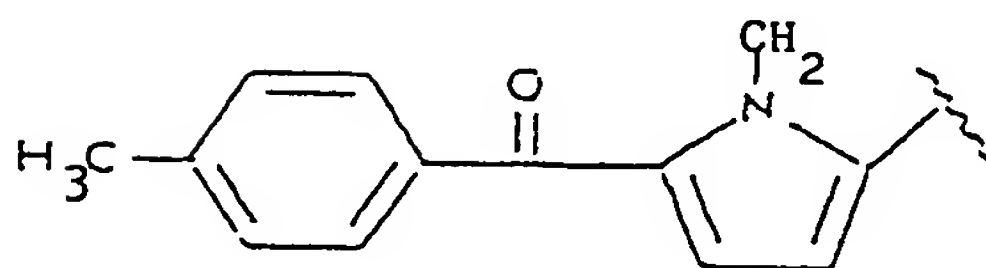
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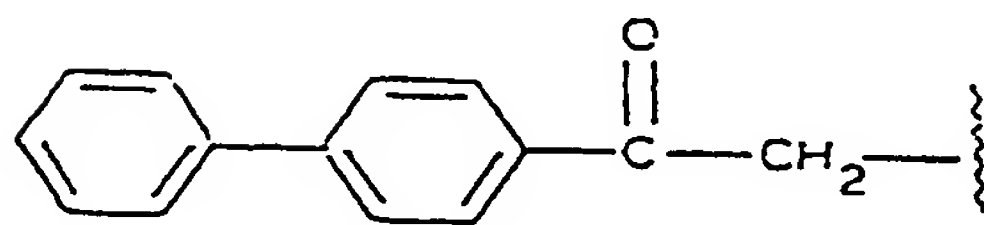
(VIII)



(IX)

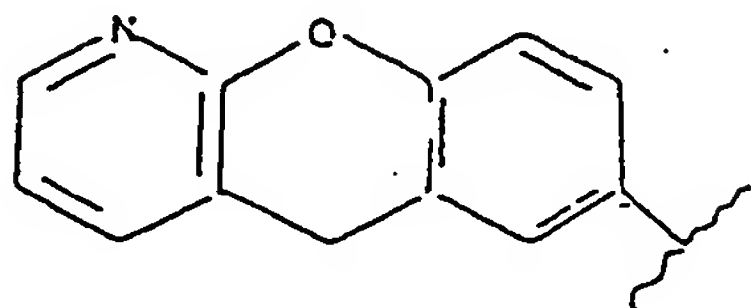


(X)

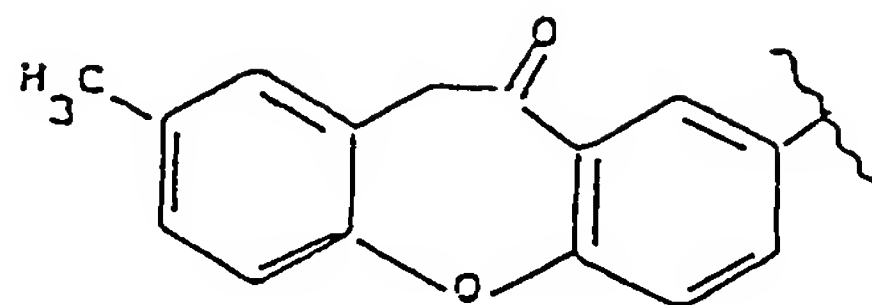


(III)

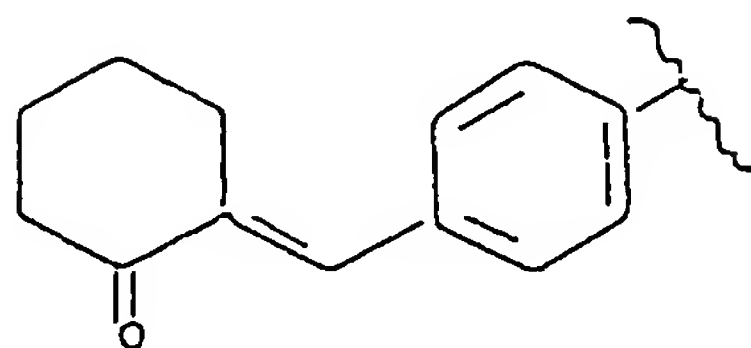
IIID) R_{1a} corresponds to the following formulas:



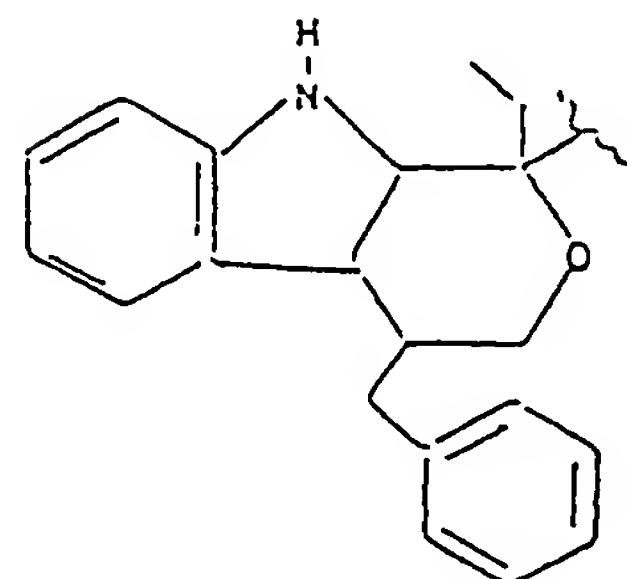
(IIIb)



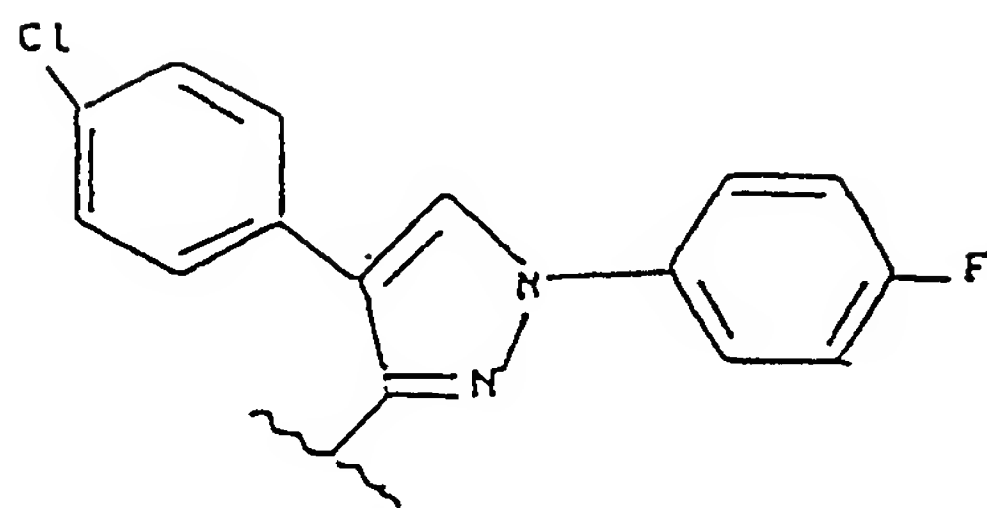
(xxx)



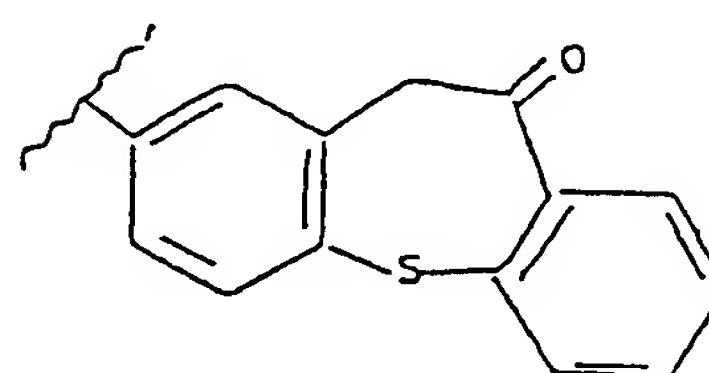
(xxxi)



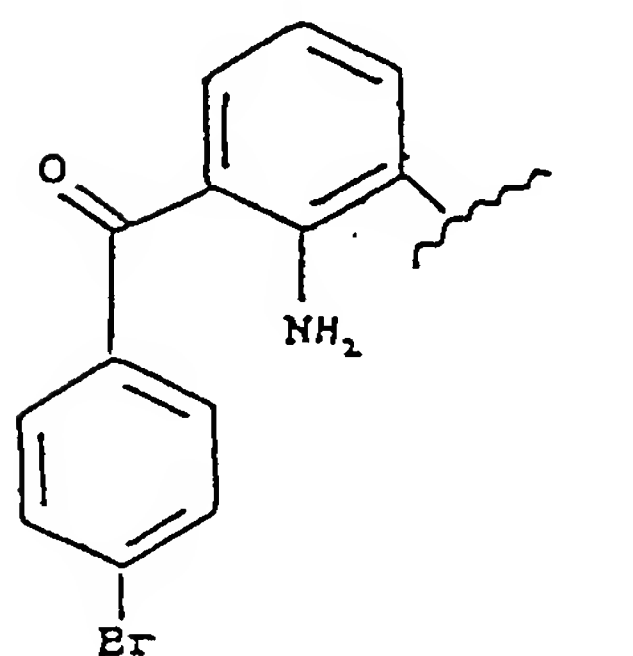
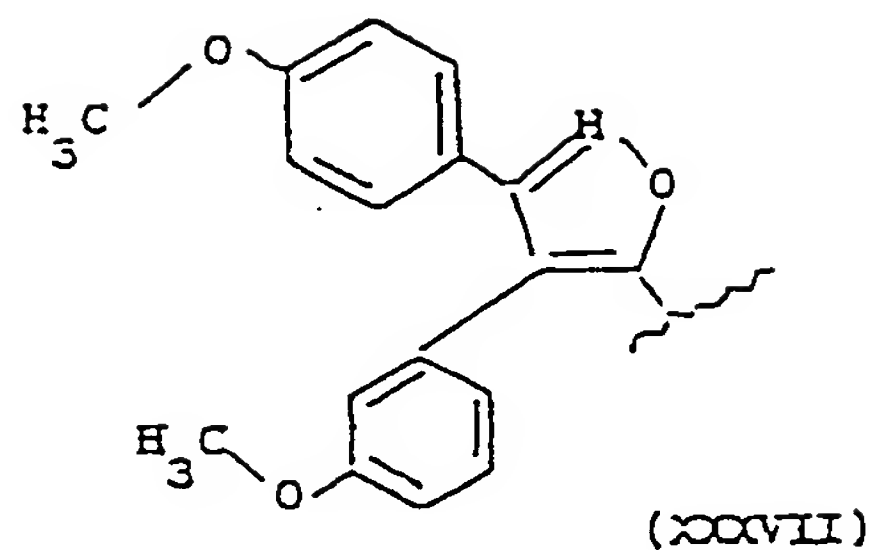
(xxxii)



(xxxiii)



(xxxvi)



wherein the meanings are the following:

when R_{1a} is as defined in formula (IV), Ketoprofen residue:

R_{III1} is H, SR_{III1} , wherein R_{III1} contains from 1 to 4 C atoms, linear or branched when possible;

R_{III2} is H, hydroxy;

preferred are the compounds wherein R_{III1} and R_{III2} are H,

R_{3a} is H, and R_{2a} is methyl, $X = O$;

when R_{1a} is as defined in formula (XXI), carprofen residue:

R_{xx10} is H, a linear or when possible branched alkyl having from 1 to 6 C atoms, a C_1 - C_6 alkoxycarbonyl bound to a C_1 - C_6 alkyl, C_1 - C_6 carboxyalkyl, C_1 - C_6 alkanoyl, optionally substituted with halogens, benzyl or halobenzyl, benzoyl or halobenzoyl;

R_{xx1} is H, halogen, hydroxy, CN, C_1 - C_6 alkyl optionally

containing OH groups, C₁-C₆ alkoxy, acetyl, benzyloxy, SR_{xx12} wherein R_{xx12} is C₁-C₆ alkyl; C₁-C₃ perfluoroalkyl; C₁-C₆ carboxyalkyl optionally containing OH groups, NO₂, amino; sulphamoyl, di-alkyl sulphamoyl with C₁-C₆ alkyl, or difluoroalkylsulphonyl with C₁-C₃ alkyl;

R_{xx11} is halogen, CN, C₁-C₆ alkyl containing one or more OH groups, C₁-C₆ alkoxy, acetyl, acetamido, benzyloxy, SR_{xx13}, being R_{xx13} as above defined, C₁-C₃ perfluoroalkyl, hydroxy, C₁-C₆ carboxyalkyl, NO₂, amino, mono- or di-alkyl-amino C₁-C₆; sulphamoyl, di-alkyl sulphamoyl C₁-C₆, or di-fluoroalkylsulphamoyl as above defined; or R_{xx11} together with R_{xx12} is a C₁-C₆ alkylene dioxy;

preferred are the compounds wherein R_{xx10} is H, the linking bridge is in position 2, R_{xx1} is H, R_{xx11} is chlorine and is in para position with respect to nitrogen;

R_{3a} is H, R_{2a} is methyl and X is O;

when R_{1a} is as defined in the formula (XXXV), residue of the tiaprofenic acid:

Ar is phenyl, hydroxyphenyl optionally mono- or poly-substituted with halogen, alkanoyl and C₁-C₆ alkoxy, C₁-C₆ trialkyl, preferably C₁-C₃, cyclopentyl, cyclohexyl cycloheptyl, heteroaryl, preferably thienyl, furyl optionally containing OH, pyridyl;

the preferred compounds of (XXXV) are those wherein Ar is phenyl, R_{3a} is H, R_{2a} is methyl and X is O;

- when R_{1a} is as defined in formula (II), suprofen residue,
of which the preferred one has been shown, wherein R_{3a} is
H, R_{2a} is methyl and $X = O$, as described and obtained in
USP 4,035,376 herein incorporated by reference;
- when R_{1a} is as defined in formula (VI), R is the residue of
indoprofen when $R_{2a} = H$ and $R_{3a} = CH_3$;
of indobufen when R_{2a} is equal to H and $R_{3a} = C_2H_5$; $X = O$,
as described and obtained according to USP 3,997,669
herein incorporated by reference;
- when R_{1a} is as defined in formula (VIII), R is the residue of
etodolac when $R_{2a} = R_{3a} = H$ and $X = O$, as described in and
obtained according to USP 3,843,681 herein incorporated
by reference;
- when R_{1a} is as defined in formula (VII), R is the residue of
fenoprofen when $R_{3a} = H$, $R_{2a} = CH_3$ and $X = O$, as described
in and obtained according to USP 3,600,437 herein
incorporated by reference;
- when R_{1a} is as defined in formula (III), R is the residue of
fenbufen when $R_{2a} = R_{3a} = H$ and $X = O$, as described in and
obtained according to USP 3,784,701 herein incorporated
by reference;
- when R_{1a} is as defined in formula (IX), R is the residue of
flurbiprofen when $R_{3a} = H$, $R_{2a} = CH_3$, $X = O$;
- when R_{1a} is as defined in formula (X) R is the residue of
tolmetin when $R_{2a} = R_{3a} = H$, $X = O$, as described in and

obtained according to FR 1,574,570 herein incorporated by reference.

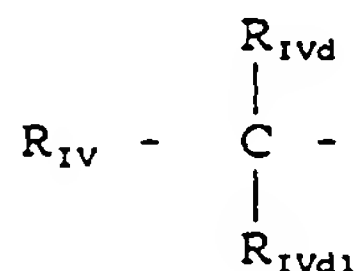
In the group IIID) R_{1a} corresponds to the following formulas: -

- IIIa), when $R_{2a} = H$ and $R_{3a} = CH_3$, the residue of pranoprofen is obtained: α -methyl-5H-[1]benzopyrano-[2,3-b]pyridin-7-acetic acid; in the preferred compound $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$.
- (XXX), when $R_{2a} = H$ and $R_{3a} = CH_3$, the bermoprofen residue is obtained: dibenz[b,f]oxepin-2-acetic acid; in the preferred compound $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$.
- (XXXI), when $R_{2a} = H$ and $R_{3a} = CH_3$, R is the radical of the compound CS-670: 2-[4-(2-oxo-1-cyclohexylidene methyl)phenyl]propionic acid; the preferred compound has $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$;
- (XXXII), when $R_{2a} = R_{3a} = H$ the Pemedolac residue is obtained; the preferred compound has $R_{2a} = R_{3a} = H$, $u = 1$ and $X = O$;
- (XXXIII), when $R_{2a} = R_{3a} = H$ the pirazolac residue is obtained: derivatives of the 4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolic acid; the preferred compounds have $R_{2a} = R_{3a} = H$, $u = 1$ and $X = O$.
- (XXXVI), when $R_{2a} = H$, $R_{3a} = CH_3$, the zaltoprofen residue is obtained; when the residue is saturated with an hydroxyl or aminic group, or with the carboxylic function

the compounds are known as dibenzothiepin derivatives; in the preferred compounds $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$.

- (XXXVII), when $R_{2a} = R_{3a} = H$ the mofezolac residue is obtained: 3,4-di(p-methoxyphenyl)isoxazol-5-acetic acid when the residue is CH_2-COOH ; in the preferred compounds $R_{2a} = R_{3a} = H$, $t = 1$ and $X = O$;
- (XII), when $R_{2a} = R_{3a} = H$ the bromfenac residue is obtained: 2-amino-3-(4-bromobenzoyl)benzeneacetic acid; the preferred compounds have $u = 1$, $t = 1$, $X = O$, $R_{2a} = R_{3a} = H$; or $t = 0$;

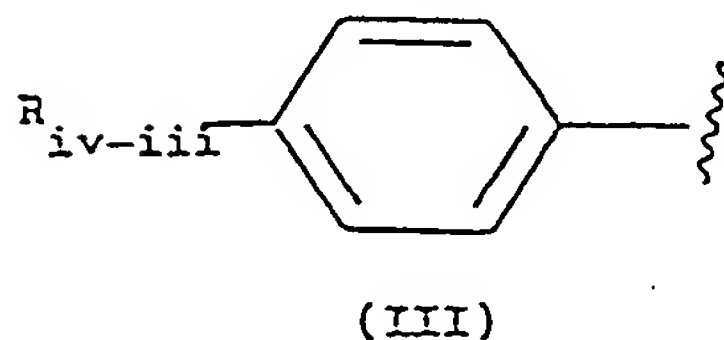
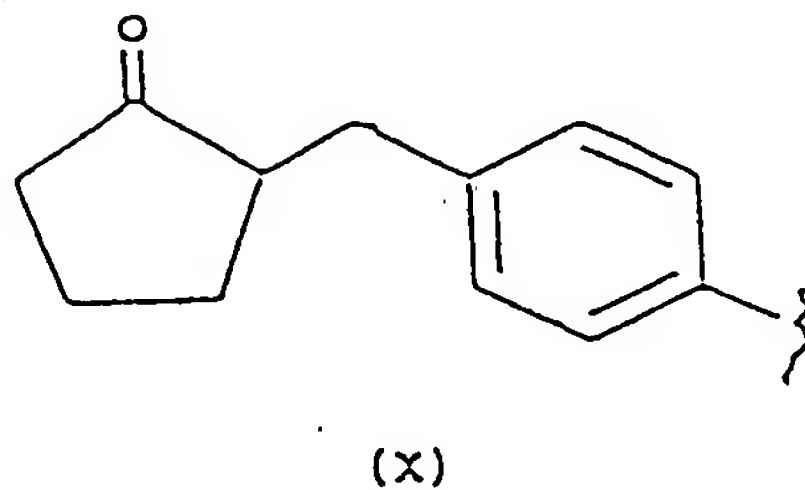
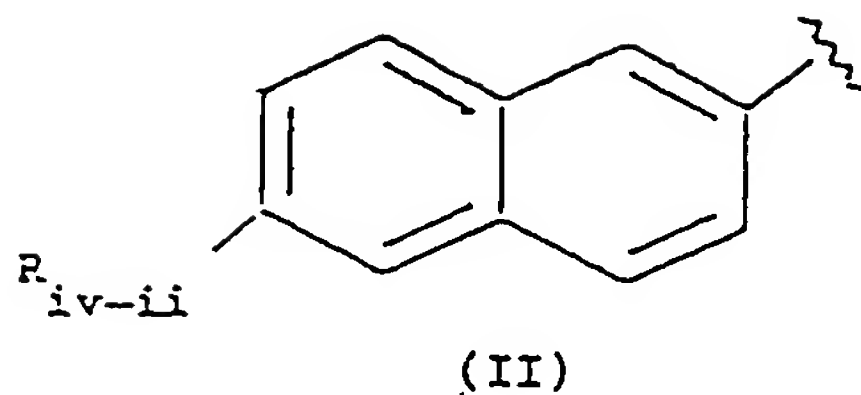
In the group IV) wherein $t = 1$, $u = 1$, R is



wherein:

R_{IVd} and R_{IVd1} are at least one H and the other a linear or branched when possible alkyl from C_1 to C_6 , preferably C_1 and C_2 , or difluoroalkyl with the alkyl having from 1 to 6 C atoms, C_1 is preferred, or R_{IVd} and R_{IVd1} form together a methylene group;

R_{IV} has the following meaning:



wherein the compounds of group IV) have the following meanings: in formula (II)

R_{iv-ii} is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_7 alkoxyethyl, C_1-C_3 trifluoroalkyl, vinyl, ethynyl, halogen, C_1-C_6 alkoxy, difluoroalkoxy, with the C_1-C_7 alkyl, C_1-C_7 alkoxyethyl, alkylthiomethoxy with the C_1-C_7 alkyl, alkyl methylthio with the C_1-C_7 alkyl, cyano, difluoromethylthio, phenyl- or phenylalkyl substituted with the C_1-C_6 alkyl; preferably R_{iv-ii} is CH_3O- , R_{Iv-d} is H and R_{Iv-d1} is CH_3 , and is known as naproxen residue;

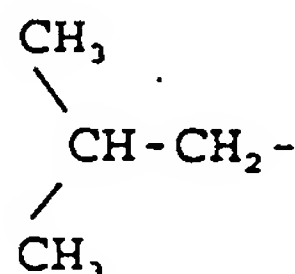
$X = O$ and X_1 is as above defined for Ia);

in formula (X), of which the loxoprofen residue has been shown, described in USP 4,161,538 herein incorporated by reference, the compounds are preferred wherein R_{Iv-d} is H and R_{Iv-d1} is CH_3 , $X = O$ and X_1 is as above defined for Ia);

in formula (III):

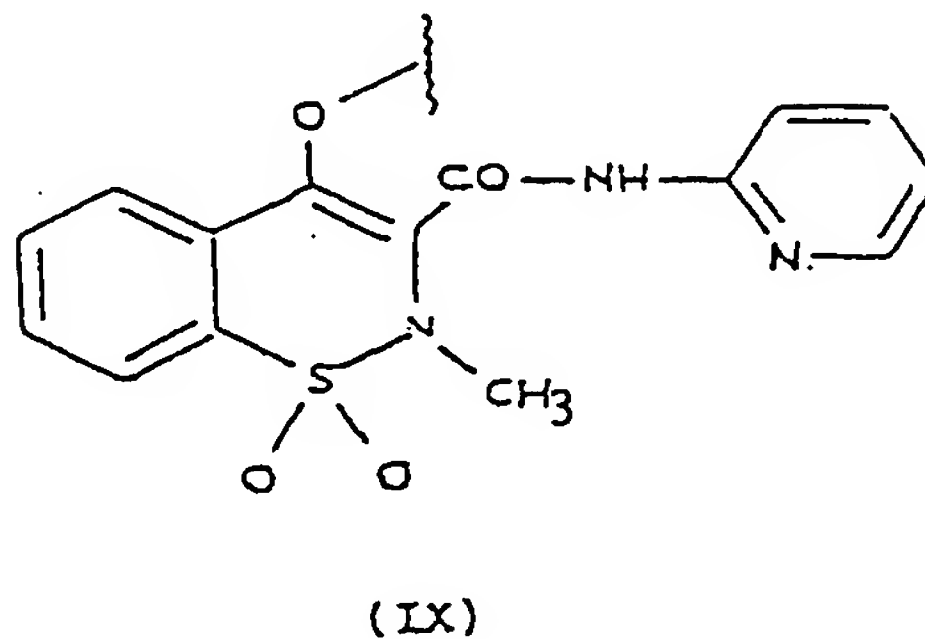
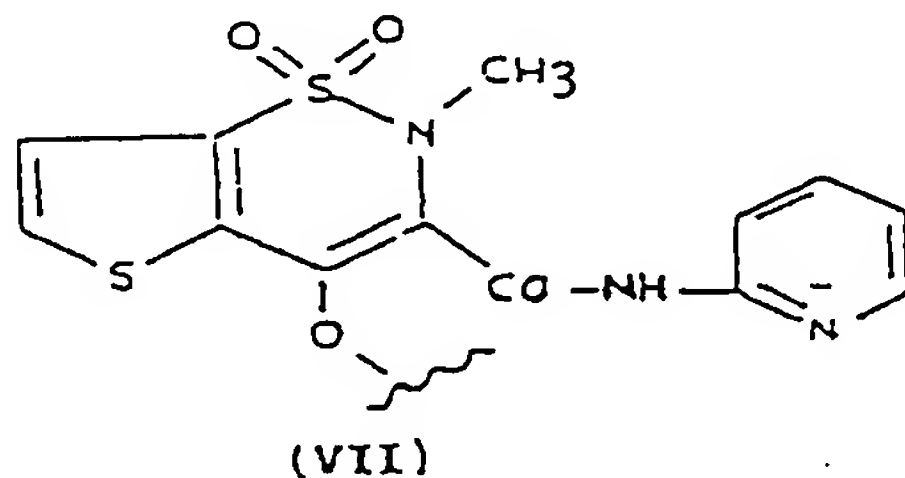
R_{IV-III} is a C_2-C_5 alkyl, optionally branched when possible, C_2 and C_3 alkyloxy, allyloxy, phenoxy, phenylthio, cycloalkyl from 5 to 7 C atoms, optionally substituted in position 1 with a C_1-C_2 alkyl;

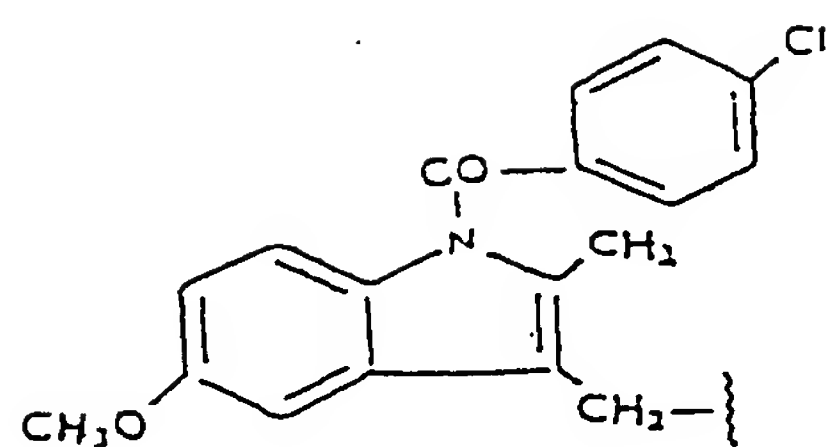
the compound in which R_{IV-III} is



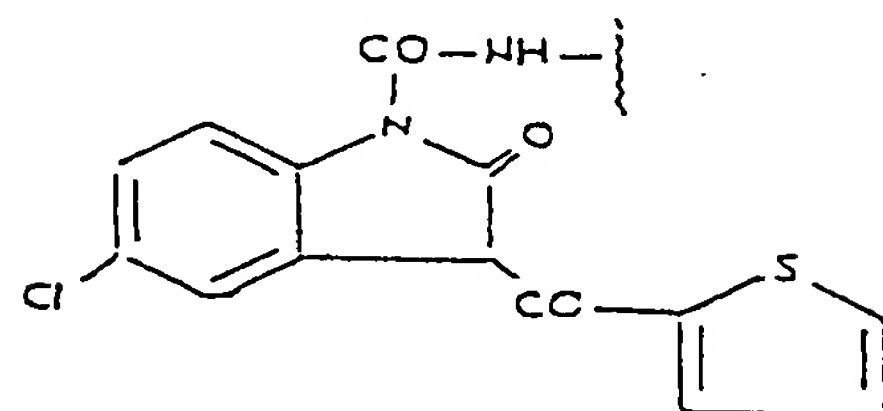
and $R_{IVd} = \text{H}$, R_{IVd1} is CH_3 , is preferred, a compound known as ibuprofen residue; $X = \text{O}$ and X_1 is as above defined for Ia);

Group V)

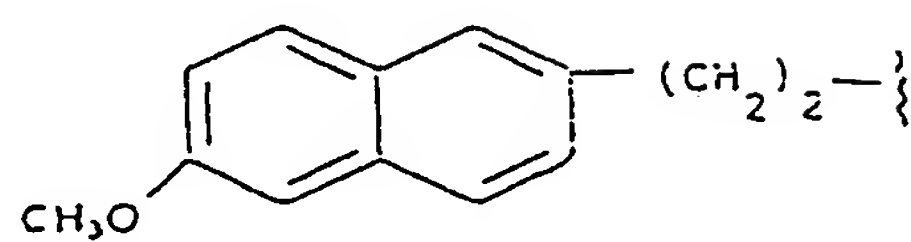




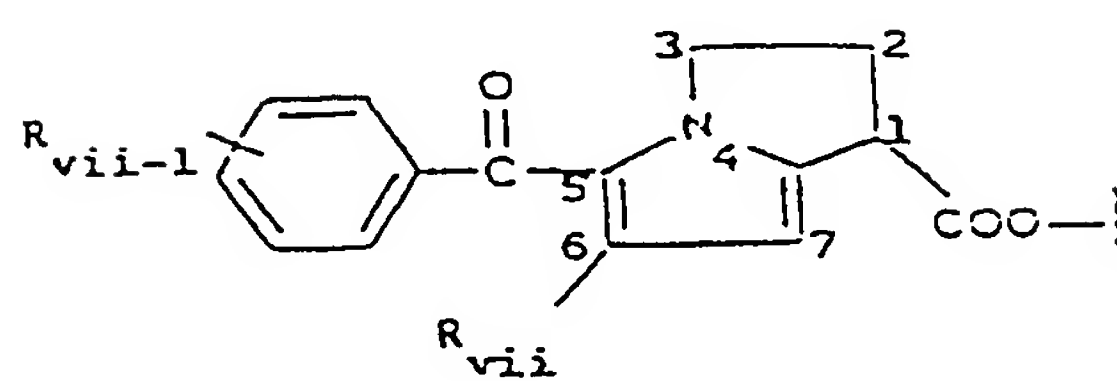
(IV)



(V)

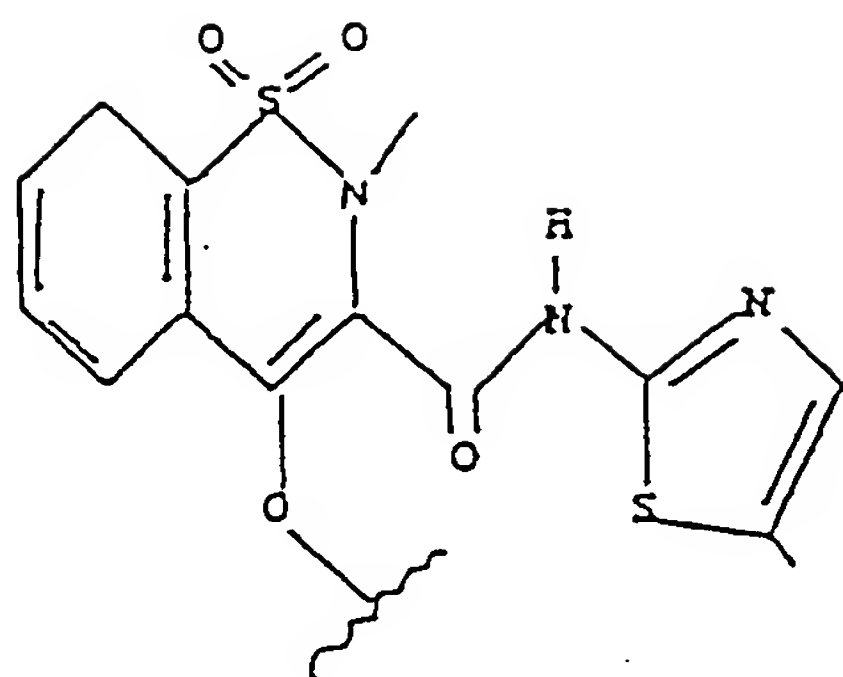


(III)

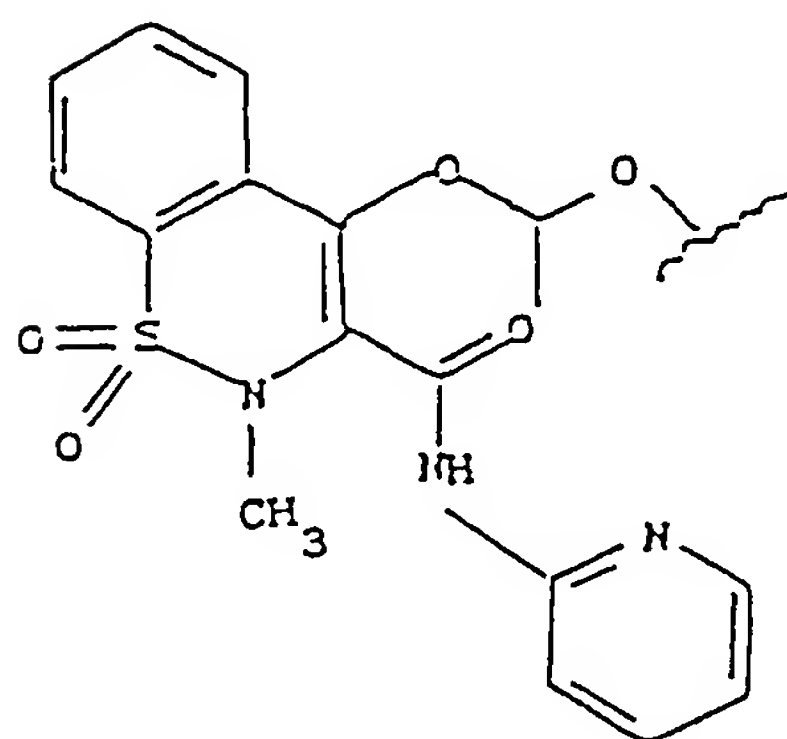


(II)

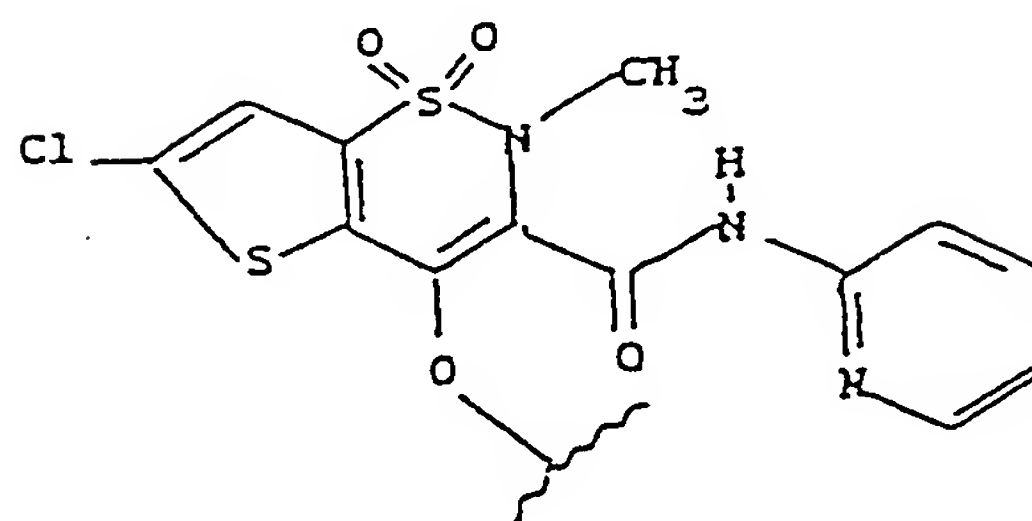
Group VE)



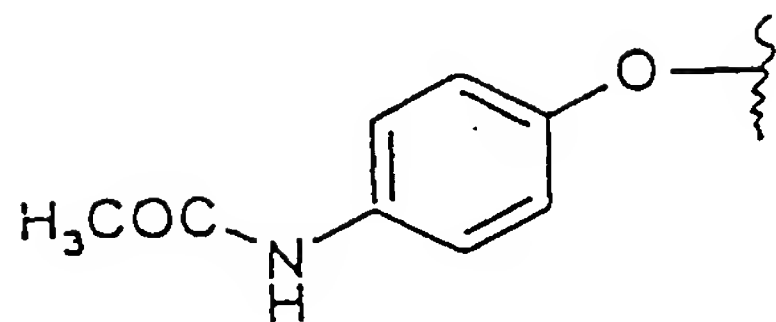
(X)



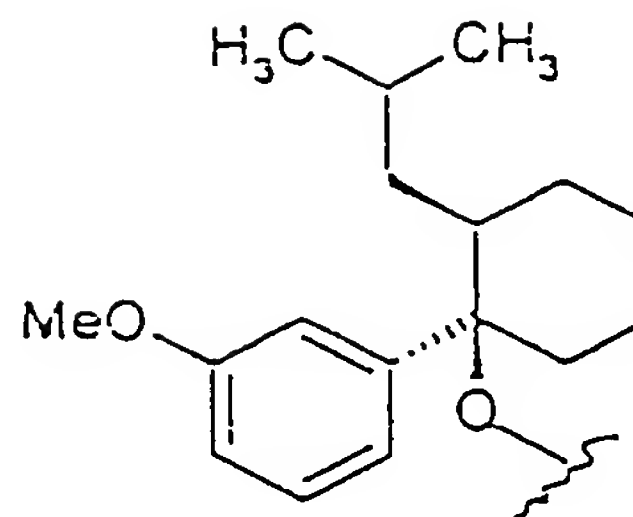
(XI)



(XIII)



(XXXIX)



(XXXXI)

In group V), the compounds have the following meanings:

when R is the formula (II),

R_{VII} is H or a linear or branched when possible C_1 - C_4 alkyl;

R_{VII-1} is R_{VII} , or a linear or branched when possible C_1 - C_4 alkoxy; Cl, F, Br; the position of R_{VII-1} being ortho, or meta, or para;

the residue of the known Ketorolac is preferred, wherein R_{VII} and R_{VII-1} are H, and $A = R$ (A being the group of the formula $A-X_1-NO_2$) and $t = 0$;

when R is the formula (V),

of which the residue of the known tenidap has been mentioned, as described and obtained in USP 4,556,672 herein incorporated by reference;

in these compounds of formula (V) $A = R$ and $t = 0$,

when R is the formula (VII),

of which the residue of the known tenoxicam has been mentioned, A is RCO, $t = 1$ $u = 0$ or A is R and $t = 0$, as

described and obtained in DE 2,537,070 herein incorporated by reference;

when R is the formula (IX),

wherein $A = R$ and $t = 0$, or $A = RCO$ with $t = 1$ and $u = 0$, the residue of the known piroxicam has been indicated, as described and obtained in USP 3,591,584 herein incorporated by reference;

when R is the formula (III)

wherein $A = RCOO$, $t = 1$ and $u = 0$ or 1 ; or $t = 0$ and $A = R$, of which the residue of the known nabumetone has been indicated, as described and obtained in USP 4,061,779 herein incorporated by reference;

when R is the formula (IV)

wherein $A = RCOO$, $t = 1$ and $u = 1$, of which the indomethacin residue has been indicated, as described and obtained in USP 3,161,654 herein incorporated by reference;

when R is the formula (X), the residue X is known as meloxicam;

the preferred compounds are those wherein $A = RCO$, $t = 1$ and $u = 0$;

when R is the formula (XI) the residue is known as ampiroxicam

when the end group is $-CH(CH_3)OCOC_2H_5$; the preferred compounds have $A = RCO$, $t = 1$ and $u = 0$;

when R is the formula (XIII) and the valence is saturated with

H

the residue derives from lornoxicam; the preferred compounds have $A = \text{RCO}$, $t = 1$ and $u = 0$;

when R is the formula (XXXX) and the valence is saturated with H

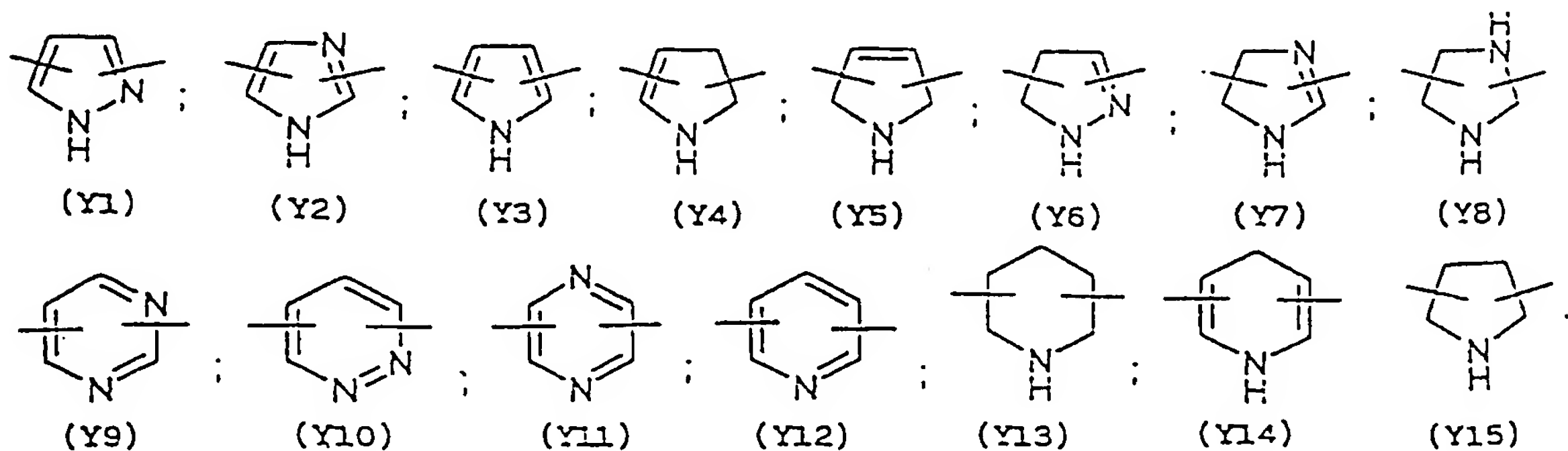
the compound known as paracetamol is obtained, as described and obtained in USP 2,998,450 herein incorporated by reference;

when R is the formula (XXXXI) and the valence is saturated with H

the compound known as Tramadol is obtained, as described and obtained in USP 3,652,589;

the preferred compounds according to the present invention obtainable with the radicals corresponding to the formulas (XXXX) and (XXXXI) have $A = \text{RCO}$, $t = 1$ and $u = 0$.

Y in the above mentioned X_1 formula contains one or two nitrogen atoms in the ring, and preferably selected from the following:



The preferred of Y is Y12 (pyridyl) substituted in position 2 and 6. The bonds can be also in non symmetric position, for example Y12 (pyridyl) can be substituted also in position 2 and 3; Y1 (pyrazol) may be 3,5-disubstituted.

The X₂ precursors, wherein the oxygen free valence is saturated with H and the free valence of the end carbon is saturated either with a carboxylic or hydroxyl group, are commercially available products or are obtainable with methods known in the prior art.

The compounds containing R of group I) of the type Ia) are described in the patent WO 92/01668 wherein the preparation methods are also described. This patent is herein incorporated by reference. The type Ib) compounds are for example prepared by using the method shown in The Merck Index, XI ed., 1989, pag. 16, No. 95 for the residue of the acetylsalicylsalicylic acid. The changes of the compounds of formula Ib) may be obtained by applying the processes mentioned in the patent WO 92/01668.

Compounds Ic) of the Ic₁) class, in which the radical is a 5-amino salicylic acid derivative (5-amino-2-hydroxybenzoic acid) known as mesalamine, when the starting radical contains -COOH, are prepared by reduction of the m-nitrobenzoic acid with Zn powder and HCl (see H. Weil et al., Ber. 55B, 2664 (1922)), or by electrolytic reduction: Le Guyader, Peltier, Compt. Rend. 253, 2544 (1961). These publications are herein

incorporated by reference.

The starting radical Ic_2), when it contains $-COOH$, is known as olsalazine: 3,3'-azabis(6-hydroxybenzoic) acid; and it is prepared according to EP 36,636 or USP 4,528,367, both herein incorporated by reference.

The Ic_3) compounds are prepared according to USP 2,396,145 herein incorporated by reference.

Equivalent compounds to Ic_1), Ic_2) and Ic_3) contain the substituents mentioned in the above references.

The compounds wherein R is of the group II) are described in the patents WO 94/04484 and USP 3,558,690 wherein the preparation methods are also described. These patents are herein incorporated by reference.

The starting compound of IIb), when the valence is saturated with $-COOH$ (flunixin), is obtained according to USP 3,337,570 and USP 3,689,653, both herein incorporated by reference. The compounds containing the substituents mentioned in the previous patents are equivalent to flunixin.

The compounds wherein R is of group III) are described and obtained with the processes mentioned in the following patents:

patent application PCT/EP/93 03193; for the compounds of formula (IV) see also USP 3,641,127; for the compounds of formula (XXI) see also USP 3,896,145; for the compounds of formula (IX) residue of flurbiprofen see also USP 3,755,427; for the

compounds of formula (II) see also USP 4,035,376; for the compounds of formula (VI) see also USP 3,997,669; for the compounds of formula (VIII) see also USP 3,843,681; for the compounds of formula (VII) see also USP 3,600,437; for the compounds of formula (III) see also USP 3,784,701.

All the above mentioned patents are herein incorporated by reference.

The processes for preparing the compounds of class IIID) are the following:

The residue IIIa) is obtained by preparing the acid compound according to USP 3,931,205, the valence is saturated with $-\text{CH}(\text{CH}_3)-\text{COOH}$. The compounds containing the substituents mentioned in the above patent are equivalent to pranoprofen. The residue (XXX) is prepared through the compound with the $-\text{CH}(\text{CH}_3)-\text{COOH}$ group (bermoprofen) according to USP 4,238,620 herein incorporated by reference. Other equivalent products are described in the above mentioned patent.

The residue (XXXI) is prepared starting from the corresponding $-\text{CH}(\text{CH}_3)-\text{COOH}$ acid according to USP 4,254,274. Equivalent compounds are described in the same patent.

The residue (XXXII) is prepared according to EP 238,226 herein incorporated by reference, when the valence is saturated with $-\text{CH}_2-\text{COOH}$. Equivalent products are reported in said patents as substituted 1,3,4,9 tetrahydropyrane [3,4-b] indol-1-acetic acids.

The residue (XXXIII) is prepared from pirazolac and the valence is saturated with $-\text{CH}_2-\text{COOH}$, as mentioned in EP 54,812 herein incorporated by reference. Equivalent products are described in said patent.

The residue (XXXVI) is prepared according to UK 2,035,311 herein incorporated by reference, starting from zaltoprofen and having the $-\text{CH}(\text{CH}_3)-\text{COOH}$ end group. Equivalent products are described in said patent.

The preparation process of the residue (XXXVII) is obtained starting from mofezolac and is prepared according to EP 26,928. Equivalent products are reported in the same patent.

The compounds in which R is of the group IV) are described in the British patent application 2,283,238, wherein also the preparation methods are indicated; this patent is herein incorporated by reference.

In the group IV) the compounds can also be obtained: for the compounds of formula (II) using USP 3,904,682; the compounds of formula (X) according to USP 4,161,538, the compounds of formula (III) according to USP 3,228,831. These patents herein mentioned are here incorporated by reference.

In the group V) the compounds can also be obtained: for the compounds of formula (II) using USP 4,089,969 herein incorporated by reference; the compounds of formula (V) can be obtained according to USP 4,556,672 herein incorporated by reference.

The residue (X) is prepared according to the German patent 2,756,113. Equivalent products are described in said patent.

The residue (XI) is prepared according to EP 147,177, herein incorporated by reference, starting from ampiroxicam having the $-\text{CH}(\text{CH}_3)\text{OCOOC}_2\text{H}_5$ end group. Equivalent products are described in said patent.

The residue (XII) is prepared according to J. Med. Chem., vol. 27 n. 11, Nov. 1984, Walsh et Al. "Antiinflammatory Agents. 3. Synthesis and Pharmacological Evaluation of 2-amino-3-benzoylphenylacetic Acid and Analogues", herein incorporated by reference. Equivalent products are described in said publication.

The residue (XIII) is prepared starting from lornoxicam, wherein the valence is saturated with H. It is prepared according to GB 2,003,877. Equivalent products are described in said patent.

Generally the connection between A and X_1 is, as seen, of ester or amidic type (NH or NR_{1c} , as defined in X) when R is of groups I, II, III, IV and V. All well known synthesis routes for forming such bonds may be used to form said connection.

In the case of esters of groups I, II, III and IV, and for the compounds of group V ending with a carboxylic function, the most direct synthetic route to obtain the corresponding nitroxyderivatives of the present invention

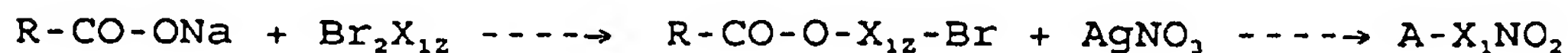
involves:

- a) reaction of the acyl chlorides $R-CO-Cl$ with halogen alcohols of the $HO-X_{12}-Cl$, $HO-X_{12}-Br$, $HO-X_{12}-I$ type, wherein X_{12} is X_1 as above defined without the oxygen atom, in the experimental conditions of the prior art, and isolation of compounds of formula $R-CO-O-X_{12}-Cl(Br, I)$. The above products can also be obtained by reaction of the sodium or potassium salts of said $R-CO-OH$ acids with dihalogen derivatives of general formula $X_{12}Cl_2$, $X_{12}Br_2$ or $X_{12}I_2$.
- b) The above products are transformed into the final products by reaction with $AgNO_3$ in acetonitrile, according to what known in the prior art.

The general schemes are the following:



wherein $X_1 = X_{12}O$.



wherein $X_1 = X_{12}O$.

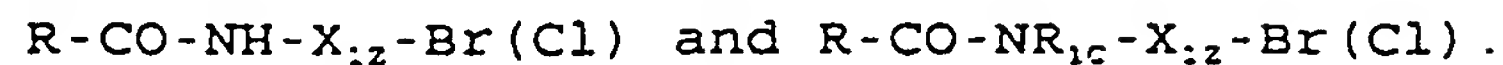
In the case of amides the synthetic sequence involves the reaction of the same acyl chlorides $RCOCl$ with aminoalcohols of general formula $NH_2-X_{12}-OH$, $NHR_{1c}-X_{12}-OH$ to give amides of general formula:



according to known methods.

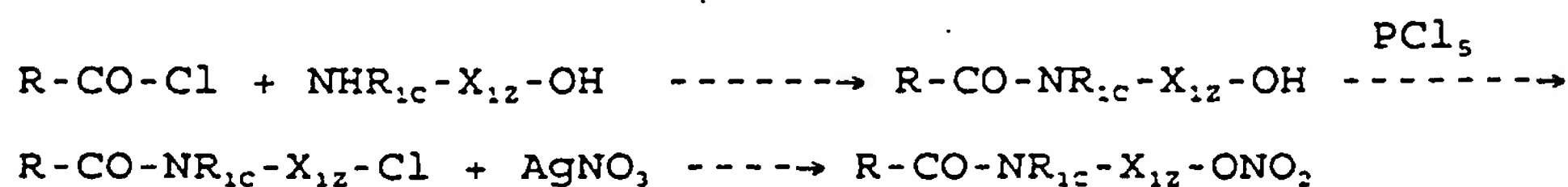
The reaction of said amides with halogenating agents such

as for example PCl_5 , PBr_3 , SOCl_2 , etc. leads to halogen derivatives of general formula:



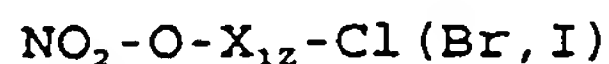
The latter by reaction with AgNO_3 in acetonitrile, according to known methods in the prior art, lead to the final products $\text{A-X}_1\text{-NO}_2$.

The synthesis scheme is the following:



wherein X_{12}O is X_1 .

- c) An alternative route to the synthesis through steps a) and b) above is the reaction of the acid sodium or potassium salts with the nitric esters of halogenoalcohols of general formula:



to give directly the nitroxy derivatives of the invention.

The reaction scheme is the following:

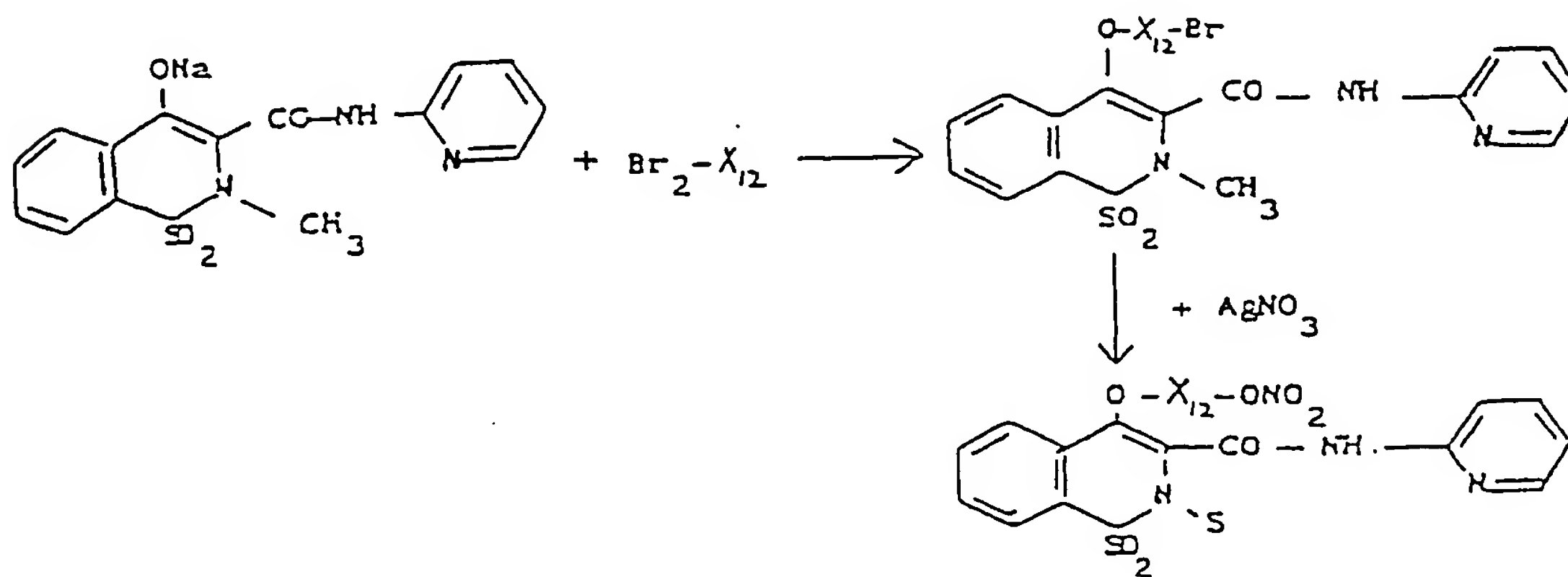


wherein X_{12}O is X_1 .

Synthetic routes similar to those above described are used for the products of group V, for example tenoxicam and piroxicam, wherein a dihalogen derivative of formula Br_2X_{12} is reacted with the corresponding enolates. The products obtained

are then transformed into the compounds of the invention by reaction with AgNO_3 in acetonitrile according to the above reported reaction scheme.

The scheme is herein reported for the piroxicam of formula IX of group V.

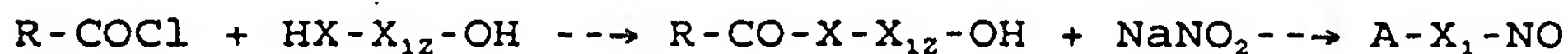


Group V products, such as tenoxicam and piroxicam, wherein the antiinflammatory reactive function is an hydroxyl, can be also reacted with an acyl chloride of formula $\text{ClCO}-\text{X}_{12}-\text{Q}_1$ wherein Q_1 is Cl, Br, I, OH. When $\text{Q}_1 = \text{OH}$, the hydroxyl is substituted with an halogen as above described before the final nitration reaction with AgNO_3 .

Nitration is carried out as above described.

In order to obtain the compounds of formula $\text{A}-\text{X}_1-\text{NO}$, acyl chlorides of formula $\text{R}-\text{COCl}$ are reacted with $\text{HX}-\text{X}_{12}-\text{OH}$, wherein R, X and X_{12} have the above mentioned meanings, in the experimental conditions described in the prior art. The obtained alcohols are reacted with sodium nitrite in a

solvent, for instance constituted of a mixture of water with tetrahydrofuran in the presence of hydrochloric acid. The reaction is described in the prior art. The general scheme is the following:



The compounds according to the present invention are transformed into the corresponding salts by reaction in organic solvent such as for example acetonitrile and tetrahydrofuran with an equimolecular amount of the corresponding organic or inorganic acid.

Examples of suitable organic acids are: oxalic, tartaric, maleic, succinic, citric acid.

Examples of suitable inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acid.

Another object of the invention is that it has surprisingly been found that the invention products containing ON-(O)₂ groups are able to exert also an inhibiting effect of the inflammation induced by liposaccharide (LPS) and therefore are usable in septic shock.

This is surprising, since it is well known that generally antiinflammatories do not meaningfully change the nitrosynthetase activity induced by lipopolysaccharides in the rat and therefore they cannot be used in septic shock.

The compounds of the present invention can be used as antiinflammatory drugs or for the therapy and prophylaxis of

cardiovascular diseases and of those pathologies wherein cellular hyperproliferation plays an important pathogenetic role.

It must be understood that when the compounds of the various groups contain at least one asymmetric carbon, the products can be used in racemic form or as single isomers. It is indeed well known that in the therapeutic uses of the invention generally an isomeric form is more active than the others. When the compounds present cis/trans isomers, they can be used in this separated form or in admixture.

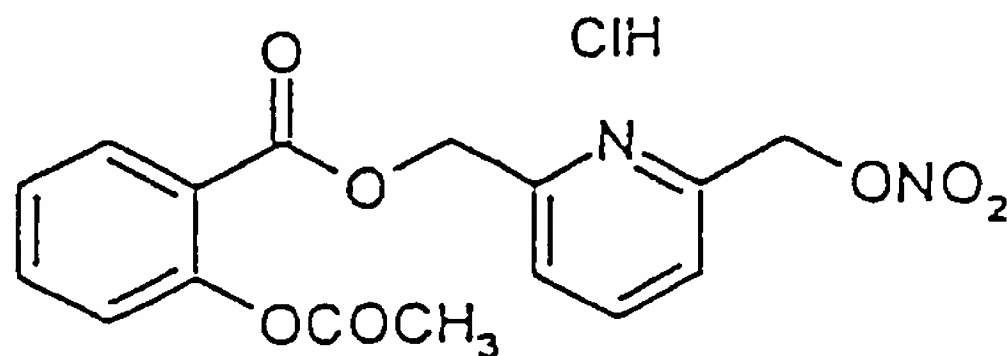
The pharmaceutical formulations of the compounds according to the present invention contain the same dose of the antiinflammatory precursor products, or lower.

The pharmaceutical formulations can be given by os or parenterally and can be prepared according to well known processes in the prior art. See the volume "Remington's Pharmaceutical Sciences".

The following Examples are given for illustrative purposes but are not limitative of the present invention.

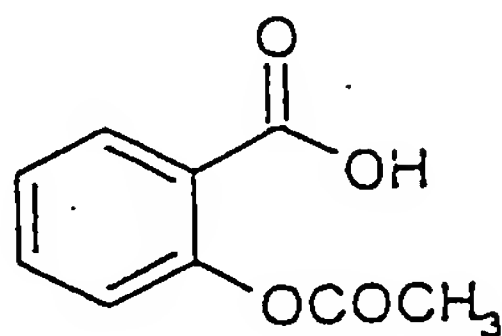
EXAMPLE 1

Synthesis of 2-acetylbenzoic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester chlorhydrate (NCX 4050) of formula:

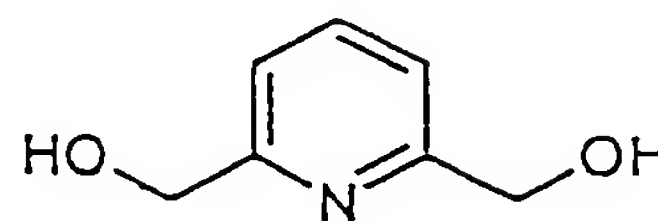


(NCX 4050)

starting from the acetylsalicylic acid (formula F1A) and 2,6-bis-(hydroxymethyl)pyridine (formula F1B)



(F1A)



(F1B)

A) -Synthesis of 2,6-bis-(chloromethyl)pyridine

To thionyl chloride (11.6 ml, 158 mmol), cooled at 0°C, 2,6-bis-(hydroxymethyl)pyridine (4 g, 28 mmol) is very slowly added. The obtained solution is left under stirring for 2 hours at room temperature, then the thionyl chloride in excess is evaporated at reduced pressure. The obtained residue is treated with chloroform and evaporated again at reduced pressure to eliminate the thionyl chloride residues. The crude product is treated with chloroform and washed with water. The organic phase is anhydri-fied with sodium sulphate and dried obtaining 4.81 g of the product as white solid having m.p. = 76°-78°C.

B) -Synthesis of 2-acetylbenzoic acid 6-(chloromethyl)-2-methylpyridinyl ester

To a solution of salicylic acid (1.6g, 8.88 mmol) in N,N'-dimethylformamide (20 ml) and under stirring sodium ethylate (0.64 g, 8.88 mmol) is added. After 30 minutes the

obtained solution is added to a solution of 2,6-bis-(chloromethyl)pyridine (4.72 g, 26.81 mmol) in N,N'-dimethylformamide (20 ml). The solution is left at room temperature for 7 days, under stirring, then is diluted with ethyl ether and washed with water. The separated organic phases are anhydri-fied with sodium sulphate and the solvent is evaporated at reduced pressure. The reaction crude product is purified by chromatography on silica gel by eluting with n-hexane/ethyl acetate 7/3. 1.7 g of the product as yellow oil are obtained. ¹H-NMR (200MHz) (CDCl₃): 8.10 (1H,d); 7.74 (1H,t); 7.57 (1H,t); 7.42 (1H,d); 7.33 (2H,m); 7.11 (1H,d); 5.42 (2H,s); 4.67 (2H,s); 2.41 (3H,s).

C) -Synthesis of 2-acetylbenzoic acid 6-(nitroxymethyl)-2-methylpyridinyl ester

To a solution of 2-acetylbenzoic acid 6-(chloromethyl)-2-methylpyridinyl ester (1.5 g, 4.7 mmol) in acetonitrile (20 ml) maintained under stirring, silver nitrate is added (1.3 g, 7.65 mmol). The solution is heated to 80°C, maintaining it sheltered from light, under stirring for 30 hours. The formed silver chloride is filtered, the solvent is evaporated. The reaction crude product is purified by silica gel chromatography by eluting with n-hexane/ethyl acetate 7/3. 1.2 g of product as yellow oil are obtained.

¹H-NMR (200MHz) (CDCl₃): 8.10 (1H,d); 7.74 (1H,t); 7.57 (1H,t); 7.42 (1H,d); 7.33 (2H,m); 7.11 (1H,d); 5.60 (2H,s); 5.42 (2H,s);

2.41 (3H, s) .

D) -Synthesis of 2-acetylbenzoic acid 6-(nitroxymethyl)-2-methylpyridinyl ester hydrochloride

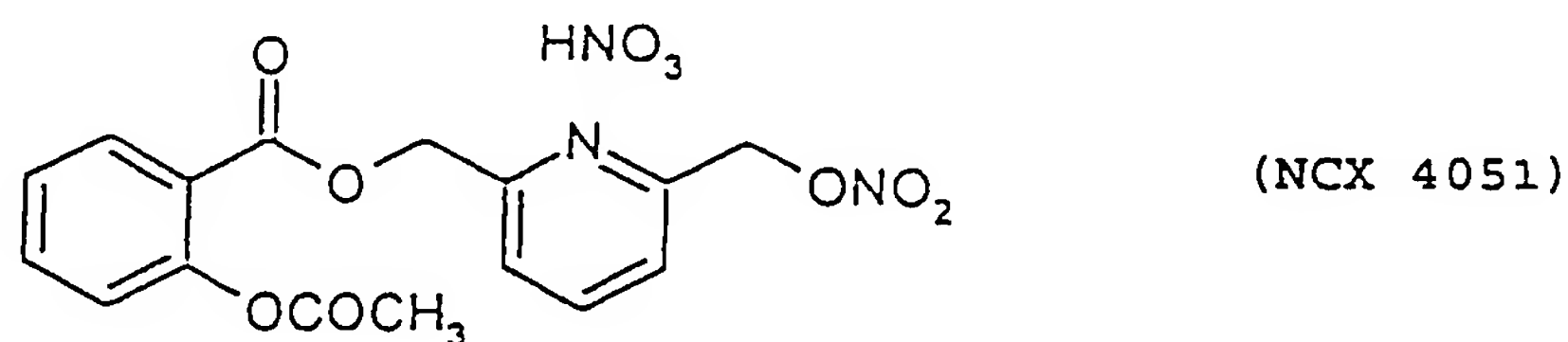
To a solution of 2-acetylbenzoic acid 6-(nitroxymethyl)-2-methylpyridinyl ester (1 g, 2.88 mmoles) in ethyl acetate (20 ml) cooled at 0°C, a solution of ethyl acetate/HCl 5M is added by dropping under stirring. It is left for one hour at 0°C, then the temperature is let reach room values. The formed precipitate is filtered and washed with ethyl ether. 900 mg of solid product are obtained.

Elementary analysis

Calculated	C 50.21%	H 3.95%	N 7.31%	Cl 9.26%
Found	C 50.23%	H 3.97%	N 7.29%	Cl 9.20%

EXAMPLE 2

Synthesis of 2-acetylbenzoic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester nitrate (NCX 4051) of formula:



starting from the 2-acetylbenzoic acid 6-(nitroxymethyl)-2-methylpyridinyl ester, isolated at step C) of the previous Example 1.

Synthesis of 2-acetylbenzoic acid 6-(nitroxymethyl)-2-methyl-

pyridinyl ester nitrate

To a solution of 2-acetylbenzoic acid 6-(nitroxymethyl)-2-methylpyridinyl ester (1 g, 2.88 mmols) in acetonitrile (10 ml) cooled at 0°C, a solution of 65% nitric acid (0.2 ml) in acetonitrile (2 ml) is added by dropping under stirring. It is left for 2 hours at 0°C, then the temperature is let reach room values. The formed precipitate is filtered and washed with ethyl ether. 1 g of solid product is obtained.

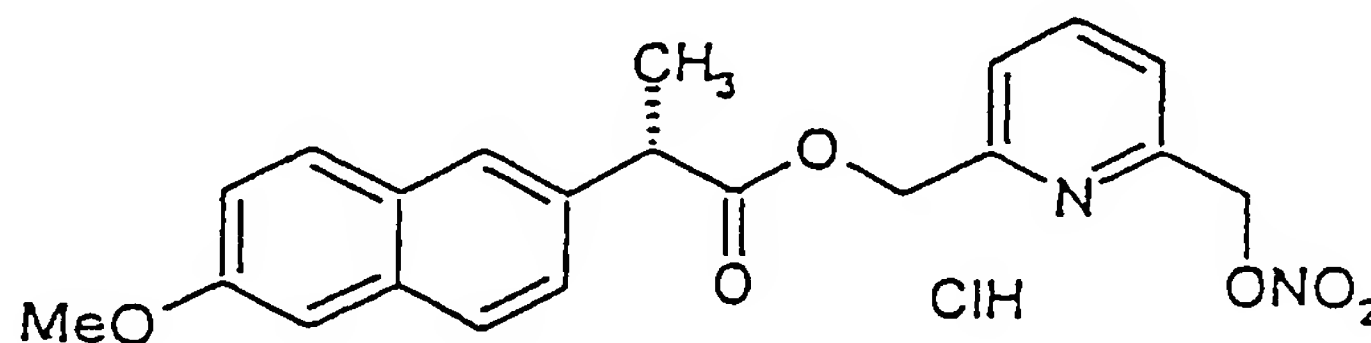
Elementary analysis

Calculated C 46.95% H 3.69% N 10.26%

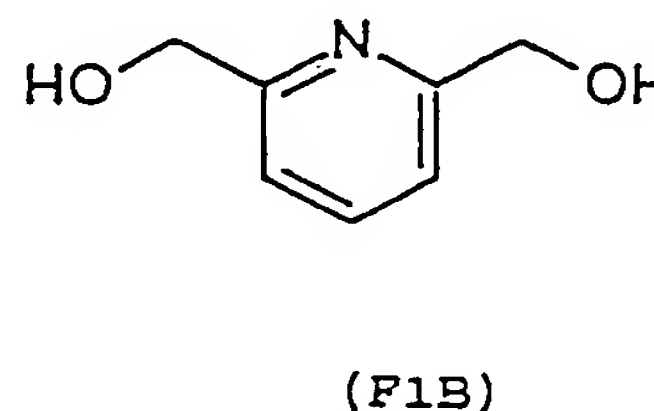
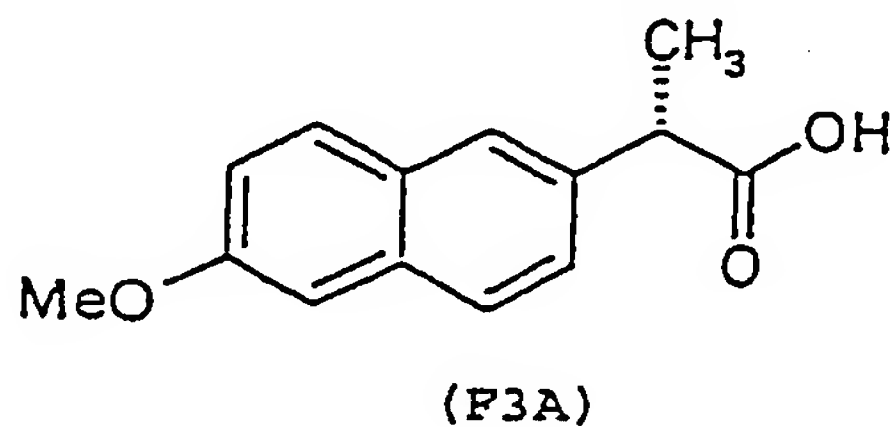
Found C 46.99% H 3.72% N 10.22%

EXAMPLE 3

Synthesis of the (S)-6-methoxy- α -methylnaphthaleneacetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester hydrochloride of formula:



starting from naproxen (formula F3A) and 2,6-bis-(hydroxymethyl)pyridine (formula F1B)



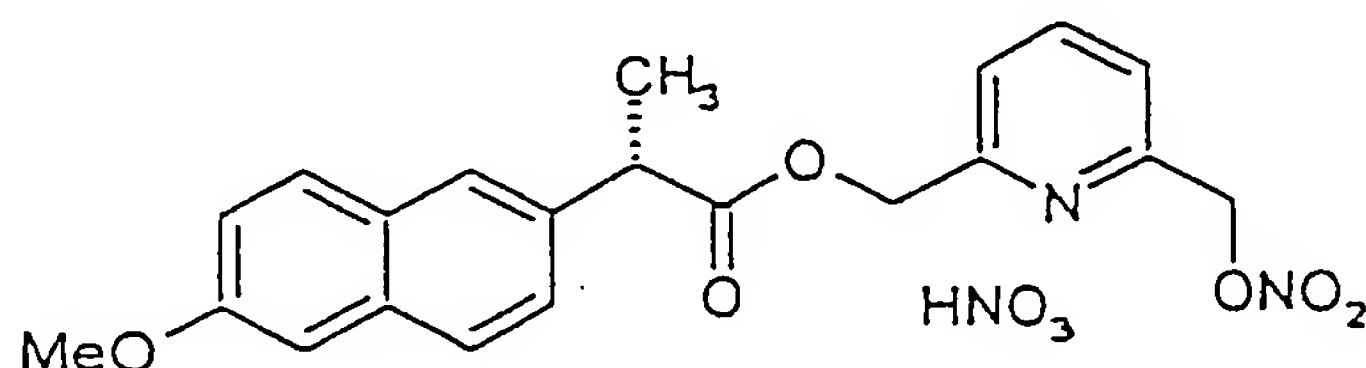
The compound is synthesized following the procedure reported in Example 1. Yield 38%.

Elementary analysis

Calculated	C 58.25%	H 4.88%	N 6.47%	Cl 8.19%
Found	C 58.29%	H 5.00%	N 6.44%	Cl 8.11%

EXAMPLE 4

Synthesis of the (S)-6-methoxy- α -methylnaphthaleneacetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester nitrate of formula:



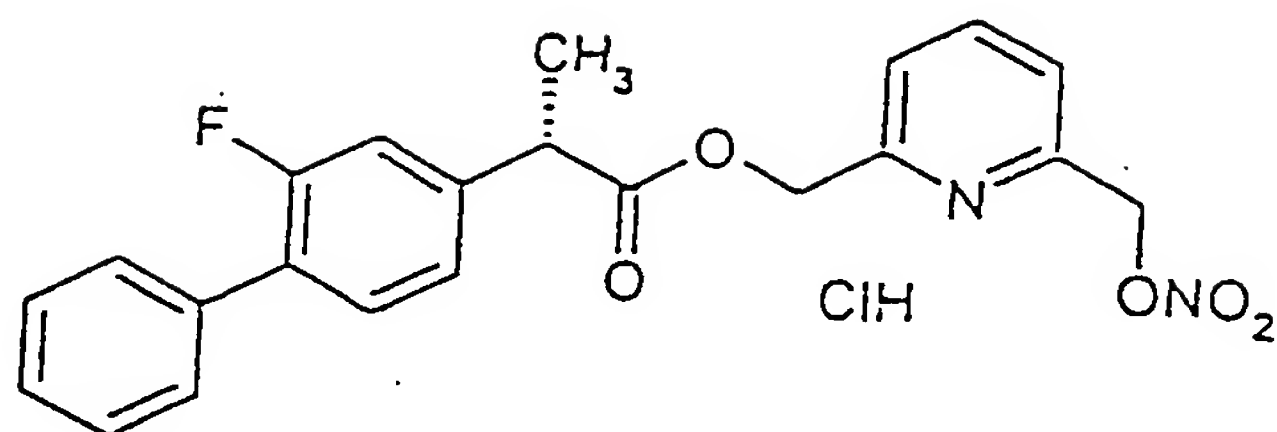
The compound is synthesized following the procedure reported in Example 2. Yield 42%.

Elementary analysis

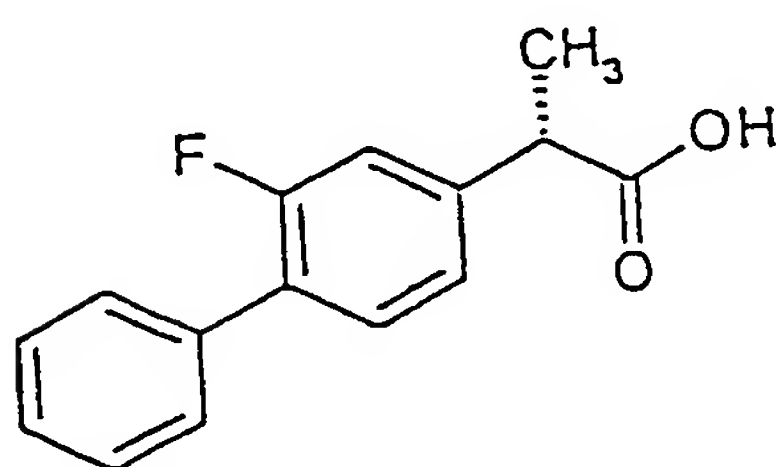
Calculated	C 54.88%	H 4.60%	N 9.15%
Found	C 54.91%	H 4.65%	N 9.10%

EXAMPLE 5

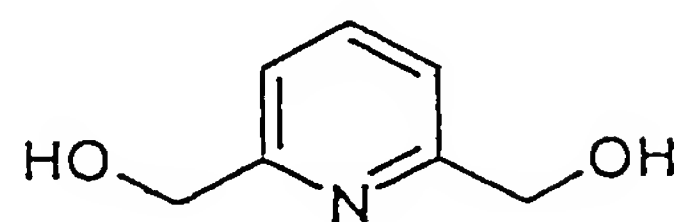
Synthesis of the 2-fluoro- α -methyl-(1,1'-biphenyl)-4-acetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester hydrochloride of formula:



starting from flurbiprofen (Formula F5A) and 2,6-bis-(hydroxymethyl)pyridine (formula F1B)



(F5A)



(F1B)

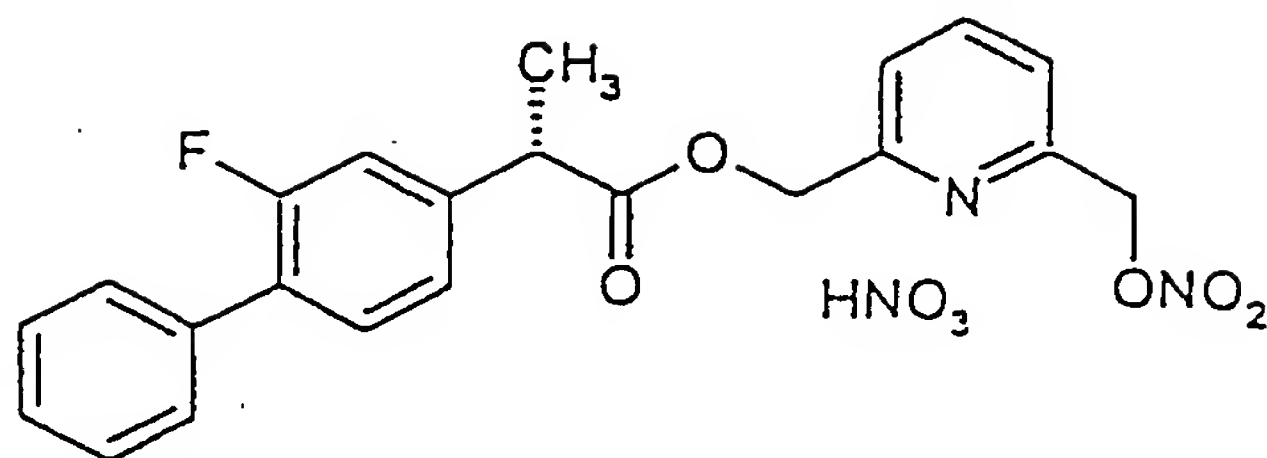
The compound is synthesized following the procedure reported in Example 1. Yield 35%.

Elementary analysis

Calculated	C 59.12%	H 4.51%	N 6.29%	Cl 7.93%	F 4.25%
Found	C 59.17%	H 4.55%	N 6.21%	Cl 7.91%	F 4.22%

EXAMPLE 6

Synthesis of the 2-fluoro-α-methyl-(1,1'-biphenyl)-4-acetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester nitrate of formula:



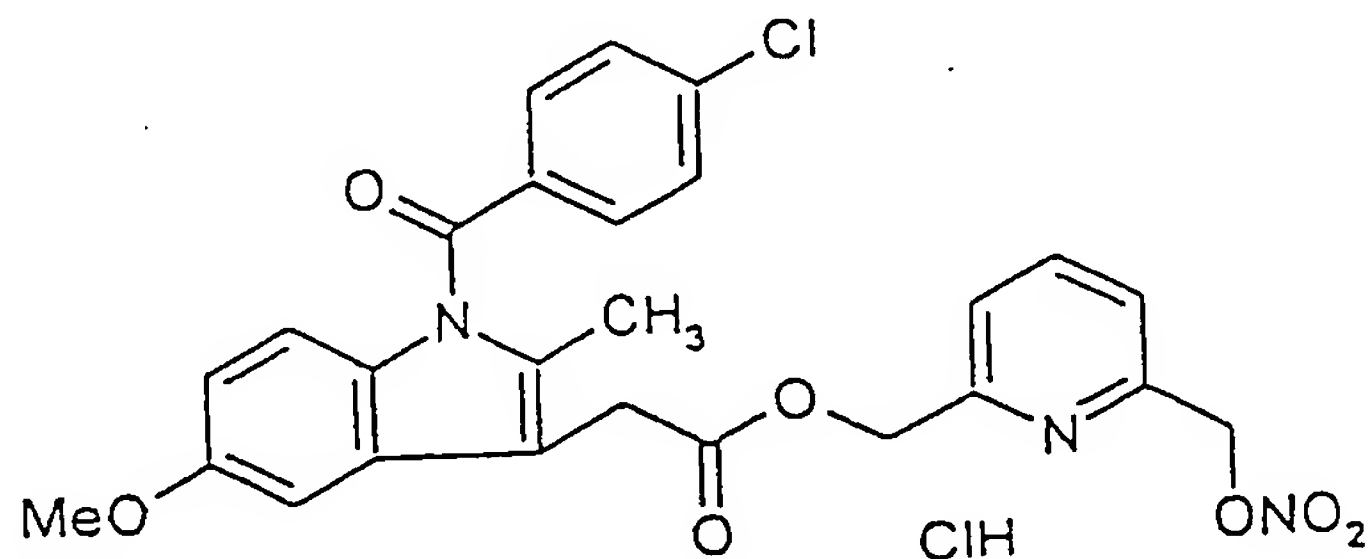
The compound is synthesized following the procedure reported in Example 2. Yield 39%.

Elementary analysis

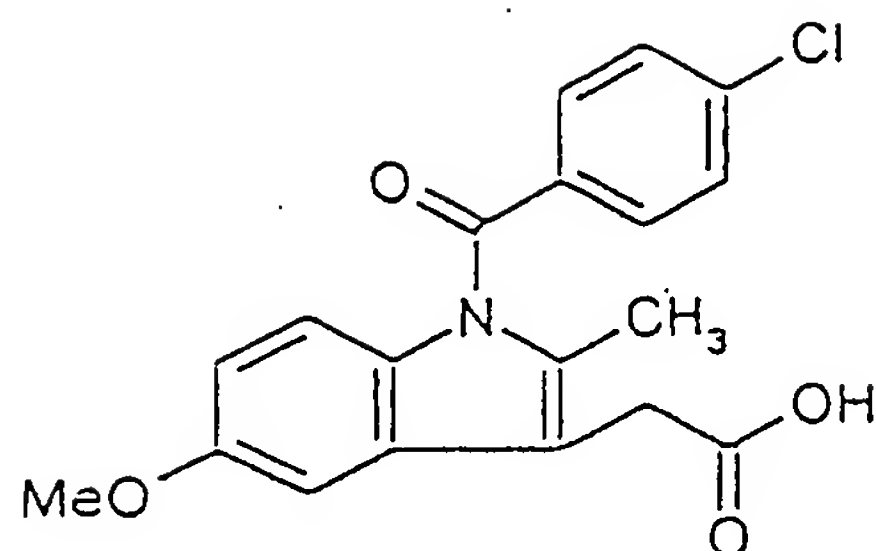
Calculated	C 55.79%	H 4.26%	N 8.91%	F 4.01%
Found	C 55.83%	H 4.30%	N 8.88%	F 4.00%

EXAMPLE 7

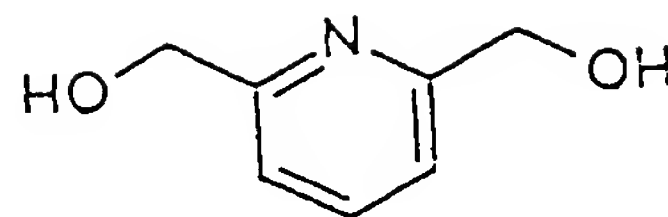
Synthesis of the 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester hydrochloride of formula:



starting from indomethacin (Formula F7A) and 2,6-bis-(hydroxymethyl)pyridine (formula F1B)



(F7A)



(F1B)

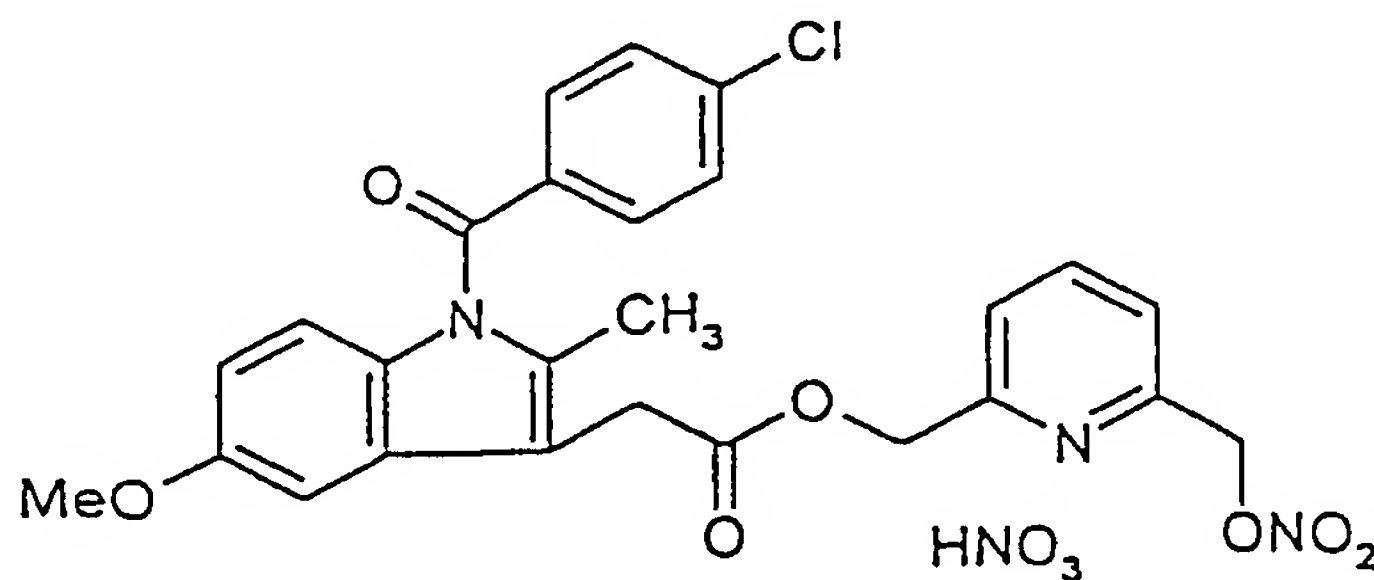
The compound is synthesized following the procedure reported in Example 1. Yield 41%.

Elementary analysis

Calculated	C 55.71%	H 4.13%	N 7.53%	Cl 12.65%
Found	C 55.73%	H 4.16%	N 7.49%	Cl 12.64%

EXAMPLE 8

Synthesis of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester nitrate of formula:



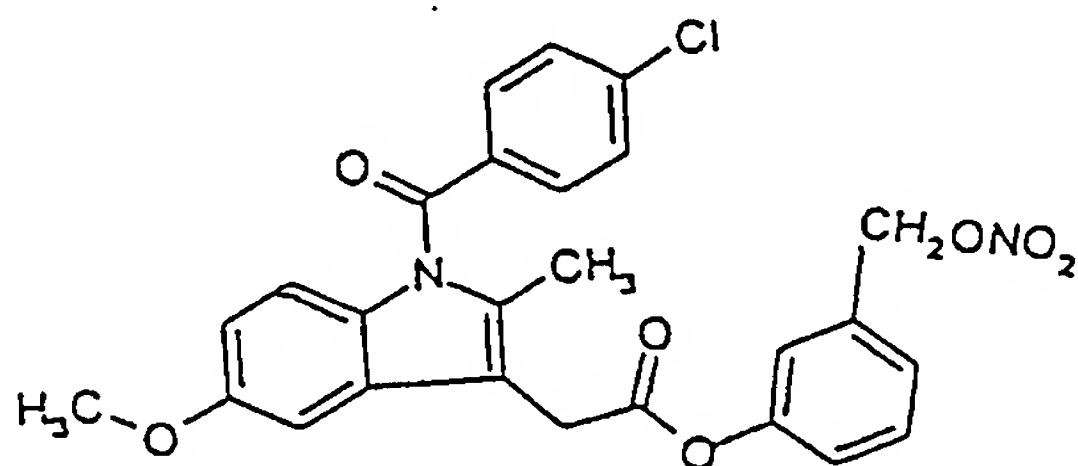
The compound is synthesized following the procedure reported in Example 2. Yield 35%.

Elementary analysis

Calculated	C 53.18%	H 3.95%	N 9.58%	Cl 6.04%
Found	C 53.20%	H 4.41%	N 9.56%	Cl 6.01%

EXAMPLE 9 (comparative)

Preparation of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 3-(nitroxymethyl)phenyl ester of formula:



wherein the precursor drug is indomethacin (formula F7A).

a) Synthesis of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 3-(formyl)phenyl ester

To a solution of 3-hydroxybenzaldehyde (g 8.30) and triethylamine (g 0.824) in methylene chloride (200 ml), cooling at a temperature in the range -5°C - 0°C indomethacin in the form of the corresponding acylchloride (g 16.50) is added under stirring. It is still maintained under stirring for 15 minutes, then water (100 ml) is added and the phases are separated. The aqueous phase is recovered and extracted with methylene chloride (300 ml). The organic phases are joined together, washed with a 5% Na_2CO_3 solution, the organic phase is anhydrified with sodium sulphate obtaining the expected

compound.

b) -Synthesis of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 3-(hydroxymethyl)phenyl ester

The compound isolated in the previous step (g 1.9) is dissolved in ethyl acetate (100 ml) in the presence of palladium 5% on carbon (g 0.290) with the 50% of humidity. The mixture is hydrogenated at room temperature and hydrogen pressure of about 2.5 atm, under stirring. After 12 hours the catalyst is removed by filtration under vacuum, washing with ethyl acetate (200 ml). The organic phases are joined together and washed with a 5% sodium bicarbonate solution and water. It is anhydriified with magnesium sulphate. It is filtered under vacuum and evaporated at reduced pressure obtaining the expected compound.

c) -Synthesis of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 3-(chloromethyl) phenyl ester

To a mixture formed by the compound isolated in the previous step (g 1.85) and thionyl chloride (ml 5.5), maintained under stirring, dimethylformamide (ml 0.5) is added at room temperature and left under stirring for one hour. At the end the thionyl chloride is evaporated at reduced pressure at a bath temperature lower than 40°C. The so obtained crude solid product is purified by crystallization with isopropyl ether (ml 30).

A solid is isolated which is dried under vacuum at room

temperature, obtaining the expected compound.

d) Synthesis of the 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 3-(nitroxymethyl) phenyl ester

A solution of the compound isolated in the previous step (1.4 g) in acetonitrile (ml 8) is treated under stirring, sheltered from light and at room temperature with AgNO₃ (g 0.9). It is heated at reflux for two hours and then cooled at room temperature and AgNO₃ (g 1.2) is added. It is filtered under vacuum, the precipitate (silver salts) is washed with acetonitrile. The organic phase is evaporated under vacuum at a bath temperature lower than 40°C. The obtained crude product is crystallized from isopropyl ether.

The process global yield is 34%. By analyzing the final product by chromatography on thin layer of silica gel, using as eluent hexane/ethyl acetate 7/3, an unitary stain is obtained. m.p. 115-117°C. ¹H-NMR (CDCl₃): 7.70 (2H, d), 7.49 (2H, d), 7.42 (1H, t), 7.14-7.06 (4H, m), 6.90 (1H, d), 6.70 (1H, dd), 5.42 (2H, s), 3.93 (2H, s), 3.86 (3H, s) 2.48 (3H, s).

EXAMPLE 10 (comparative)

Synthesis of the 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 4-nitroxybutyl ester

To a solution of indomethacin (5.04 g, 14 mmol) in chloroform (50 ml) at room temperature 1-chloro-4-butanol (1.4 ml, 14 mmol), N,N' dicyclohexylcarbodiimide (2.87 g, 14 mmol) and 4-dimethylaminopyridine (0.11 g, 0.09 mmol) are

added. The mixture is maintained under stirring at room temperature for 6 hours. The solid is filtered and the organic phase is washed with water, separated, dried with sodium sulphate and finally evaporated under vacuum. The obtained residue is purified by column chromatography (eluent n-hexane/ethyl acetate 9/1). An yellow-coloured oily residue (5.2 g), corresponding to 4-chlorobutyl ester of the indomethacin is isolated.

5 g of the compound (11 mmoles) are dissolved in acetonitrile (25 ml) and treated with silver nitrate (3.8 g, 22 mmoles). The mixture is let reflux in the dark for 48 hours. After cooling, the solid residue is filtered and the solvent is evaporated under vacuum. The obtained residue is purified by column chromatography (eluent n-hexane/ethyl acetate 9/1). At the end an oil (4.2 g) is isolated.

¹H-NMR (CDCl₃, ppm): 7.65 (2H, m); 7.45 (2H, m); 6.95 (1H, d); 6.84 (1H, d); 6.66 (1H, dd); 4.10 (2H, t); 3.82 (3H, s); 3.65 (2H, s); 3.35 (2H, t); 2.39 (3H, s); 1.80 (4H, m).

EXAMPLE 11

Solubility tests

Solubility tests in water of the salts of the 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester (Ex. 7 and 8) by comparison with the 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 3-(nitroxymethyl)phenyl ester (Ex. 9) and

with the 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 4-nitroxybutyl ester have been carried out.

Said solubility tests have been effected by adding, at room temperature, in a 50 ml flask, 5 g of the substance and then bringing to volume with water.

The compounds according to the invention completely dissolve, therefore they show a solubility equal to at least 100 mg/ml.

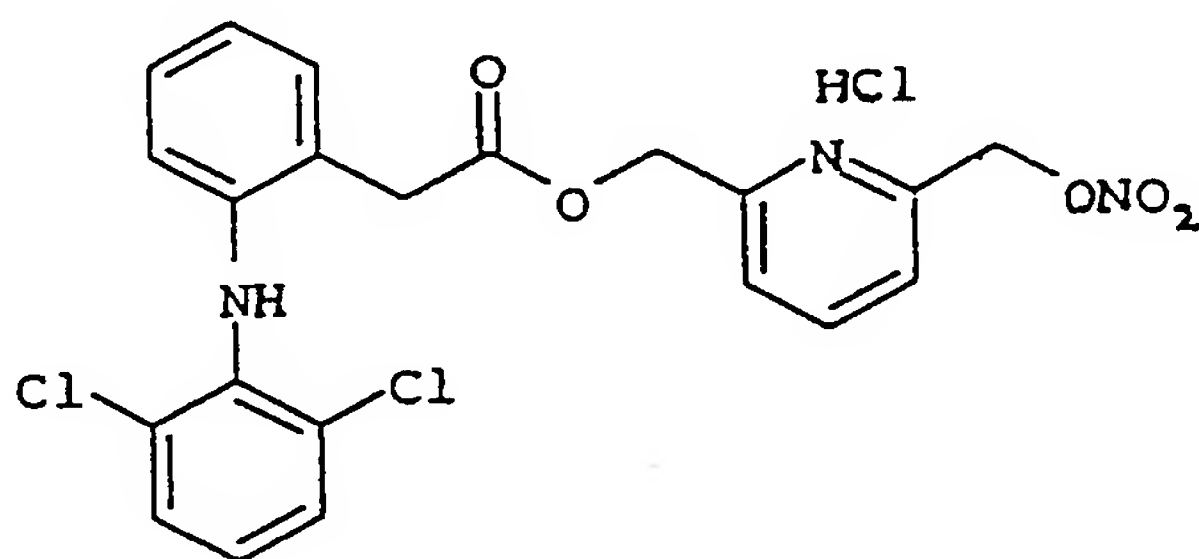
The comparative compounds under the same conditions are unsoluble.

EXAMPLE 12

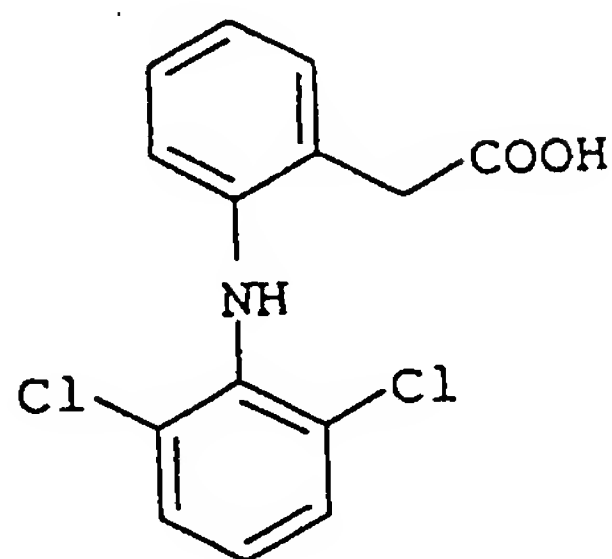
Example 11 has been repeated with the compounds from 1 to 6. All the compounds result soluble in water under the same conditions of the previous Example.

EXAMPLE 13

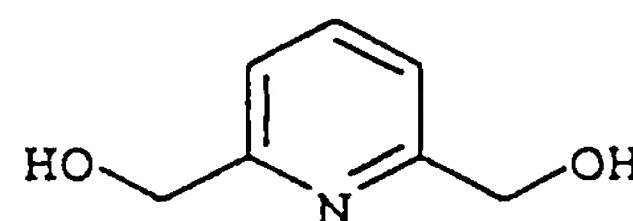
Synthesis of 2-[(2,6-dichlorophenyl)aminobenzeneacetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester hydrochloride of formula:



starting from 2-[(2,6-dichlorophenyl)aminobenzeneacetic acid sodium salt (formula) and 2,6-bis-(hydroxymethyl)pyridine



(F9A)



(F1B)

A) Synthesis of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(chloromethyl)-2-methylpyridinyl ester

To a solution of 2,6-bis-(chloromethyl)pyridine (3.83 g, 21.75 mmol), prepared as described in Example 1 A, in N,N'-dimethyl formamide (20 ml), under stirring, a solution of 2-[(2,6-dichloro phenyl)amino]benzene acetic acid sodium salt (3.04 g, 9.54 mmol) in N,N'-dimethylformamide (25 ml) is added dropwise. The solution is stirred at room temperature for one day, then it is diluted with ethyl acetate and washed with water. The organic phases are recovered and anhydriified with sodium sulphate. The solvent is then evaporated under a reduced pressure. The crude reaction product is purified by chromatography on a silica gel column, eluted with n-hexane/

ethyl acetate 8/2. 2.88 g of the product are obtained as a white solid. Yield 69%

¹H NMR (200MHz) (CDCl₃): 7.66 (1H, t); 7.41 (1H, d); 7.33 (1H, d); 7.27 (1H, d); 7.18 (2H, m); 6.97 (2H, dd); 6.81 (1H, s); 6.57 (1H, d); 5.3 (2H, s); 4.62 (2H, s); 3.93 (2H, s).

B) -Synthesis of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(nitroxymethyl)-2-methyl pyridinyl ester

To a stirred solution of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(chloromethyl)-2-methylpyridinyl ester (2.438 g, 5.59 mmol) in 90 ml of acetonitrile is added silver nitrate (2.19 g, 12.89 mmol). The solution is further stirred for 30 hours at 80°C maintaining it sheltered from light. The formed silver chloride is filtered and the solvent evaporated. The crude reaction product is purified by silica gel column chromatography, eluted with n-hexane/ethyl acetate 7/3. 1.2 g of the product in the form of a yellow oil are obtained. Yield 46%.

¹H NMR (200MHz) (CDCl₃): 7.69 (1H, dd); 7.33 (1H, d); 7.25 (1H, m); 7.23 (2H, m); 7.16 (1H, dd); 6.98 (2H, m); 6.82 (1H, s); 6.57 (1H, d); 5.49 (2H, s); 5.31 (2H, s); 3.94 (2H, s).

C) -Synthesis of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(nitroxymethyl)-2-methyl pyridinyl ester hydrochloride

To a solution of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(nitroxymethyl)-2-methylpyridinyl ester (0.400 g, 0.86 mmol) in ethyl acetate (6 ml), cooled at 0 °C, a

solution of HCl/ ethyl acetate 3M (0.6 ml) is added dropwise under stirring. the reaction mixture is stirred for one hour at 0 °C, then is warmed up to room temperature.

The formed precipitate is filtered and washed with ethyl ether. 0,310 g of solid product are obtained. Yield 73%.

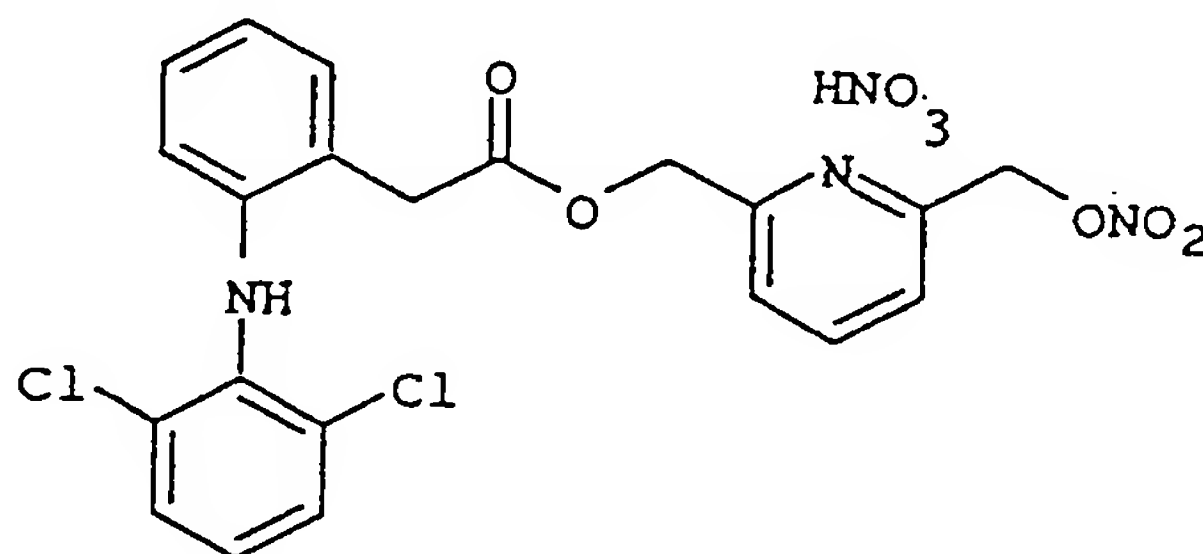
Elementary analysis

Calculated: C 50.58% H 3.63% N 8.42% Cl 21.32%

Found: C 50.62% H 3.66% N 8.40% Cl 21.02%

EXAMPLE 14

Synthesis of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid
6-(nitroxymethyl)-2-methyl pyridinyl ester nitrate of formula:



starting from 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(nitroxymethyl)-2-methylpyridinyl ester, obtained in step B) of the previous example 13.

Synthesis of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid
6-(nitroxymethyl)-2-methyl pyridinyl ester nitrate

To a solution of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(nitroxymethyl)-2-methylpyridinyl ester (0.760 g, 1.65 mmol) in acetonitrile (6 ml), cooled at 0 °C, a solution of nitric acid (65%) (0.150 ml) in acetonitrile (2 ml) is added dropwise, under stirring. The reaction mixture is stirred one hour at 0 °C, then is warmed up to room temperature. The formed precipitate is filtered and washed with ethyl ether. 0.600 g of the product, in the form of a solid, are obtained. Yield 70%.

Elementary analysis

Calculated: C 48.02% H 3.45% N 10.67% Cl 13.50%

Found: C 48.06% H 3.47% N 10.66% Cl 13.60%

EXAMPLE 15

Study of the inhibition effect on smooth muscle contraction and smooth muscle cell proliferation

As known, contraction and/or cell proliferation of smooth muscle are important steps in the inflammation process.

Smooth muscle contraction

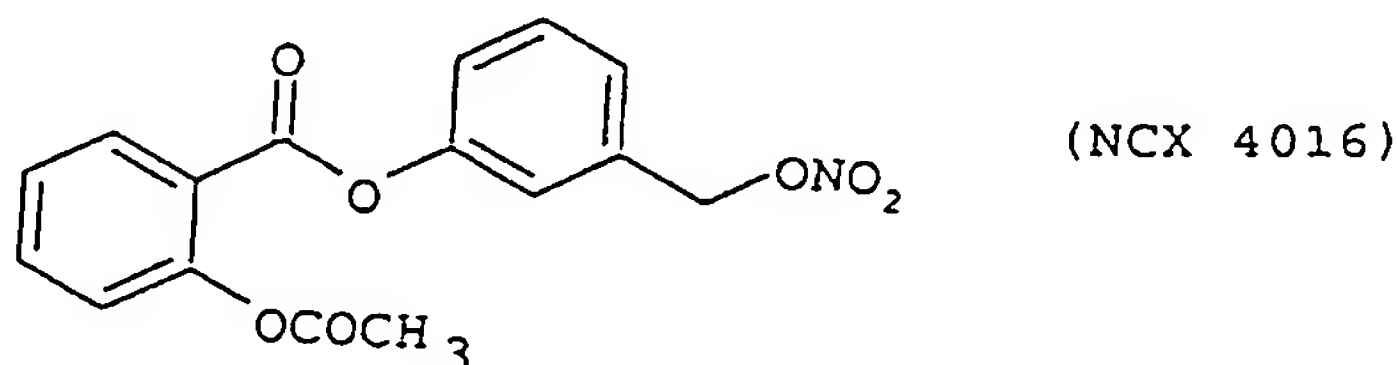
New Zealand White Rabbits (2.0-2.5 kg) were killed by cervical dislocation, cavernosal tissue (corpus cavernosus) and aorta excised.

The tissue was mounted in organ baths for recording of isometric tension, according to the method described by Khan MA et al (BJU Int. 1999 84(6):720-4). Tissues were pre-contracted with phenylephrine (10 μ M) and relaxation responses

to carbachol assessed in the presence of the compound to be tested.

The compound of the invention used in the assay was 2-acetylbenzoic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester hydrochloride (NCX 4050), which synthesis is described in preceding example 1.

The reference compound was 2-acetoxybenzoic acid (3-nitroxymethyl)phenyl ester of formula



which synthesis is described in ex. 3 of the PCT patent application WO 97/16405 filed in the Applicant's name.

Results are given in following Table 1, that show that the compound of the invention is more active than the reference compound in inhibiting smooth muscle contraction.

Smooth muscle cell proliferation

Human saphenous veins were cultured by standard explant methods (J. Cardiovasc. Pharmacol. 1999, 33(2), 204-11). Tissues were collected into sterile pots containing PBS, penicillin and streptomycin. Under sterile tissue culture conditions, tissues were cut into small pieces (approximately

1 mg weight) and placed into a standard culture medium containing 20 % fetal calf serum (FCS) for several days (medium changed every 2-4 days). ³H-thymidine was measured in the DNA fraction of cells cultured into 48 well plates. Cells were cultured to confluence in the medium containing 10% FCS. Cells were deprived of serum for 24 h before the addition of 10% FCS, together with different concentration of steroids. After 24 h, ³H-thymidine was added to the cells for 4 h. Cells were washed with phosphate buffered saline and ethanol. DNA was extracted with sodium hydroxide solution and the ³H material counted by scintillation. The data represents observations made in triplicate wells.

Table 2 reports results obtained on the inhibitory effect of the tested compounds on human vascular smooth cell proliferation.

The Table shows that the compound of the invention is much more active than the reference compounds.

Table 1 and 2 demonstrate that the antiinflammatory activity of the compound of the invention is higher than that of the reference compound.

Table 1

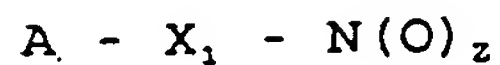
Inhibition of aorta and corpus cavernosum smooth muscle contraction at different concentrations (10^{-4} and 10^{-5} M) of the compound of the invention (NCX 4050) and of the reference compound (NCX 4016)			
sample	concentration (log M)	% inhibition rabbit aorta	% inhibition rabbit corpus cav.
NCX 4050	- 4	87	85
	- 5	80	63
NCX 4016 (comp.)	- 4	20	47
	- 5	18	14

Table 2

Inhibition of smooth muscle cell proliferation at different concentrations (10^{-4} and 10^{-5} M) of the compound of the invention (NCX 4050) and of the reference compound (NCX 4016)		
sample	concentration (log M)	% inhibition cell proliferation
NCX 4050	- 4	95
	- 5	82
NCX 4016 (comp.)	- 4	60
	- 5	43

CLAIMS

1. Organic or inorganic salts of compounds of general formula:

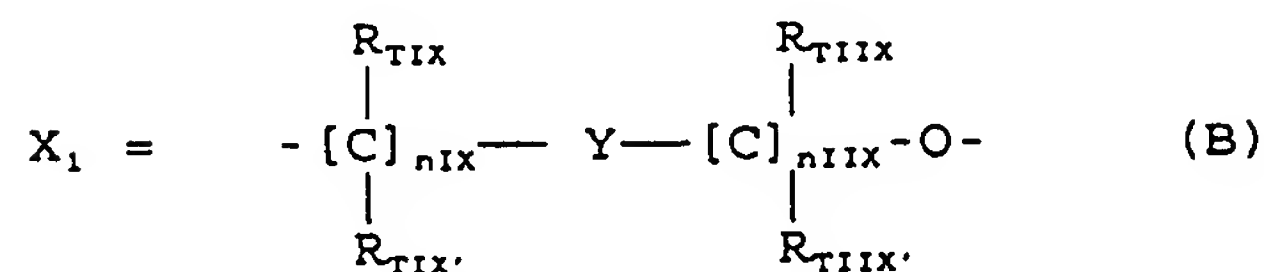


wherein:

z is an integer and is 1 or 2;

A = $R(COX_u)_t$ and wherein t is an integer 0 or 1; u is 0 or 1;

X = O, NH, NR_{1c} wherein R_{1c} is a linear or branched C_1 - C_{10} alkyl.



wherein:

nIX is an integer between 0 and 3;

nIIX is an integer between 1 and 3;

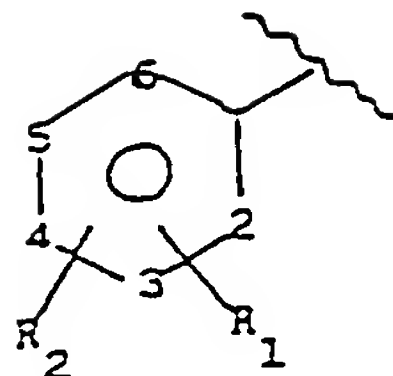
R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$, equal to or different from each other, are H or a linear or branched C_1 - C_4 alkyl;

Y is a ring containing at least one salifiable nitrogen atom; preferably Y is an heterocyclic ring, saturated or unsaturated or aromatic, having preferably 5 or 6 atoms and containing at least one or two nitrogen atoms;

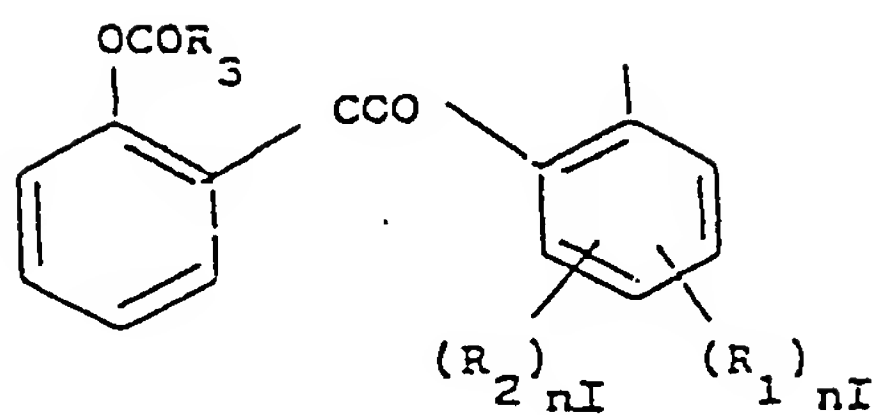
R is selected from the following groups:

Group I) wherein t = 1 and u = 1

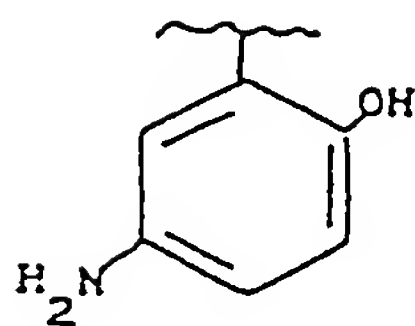
Ia)



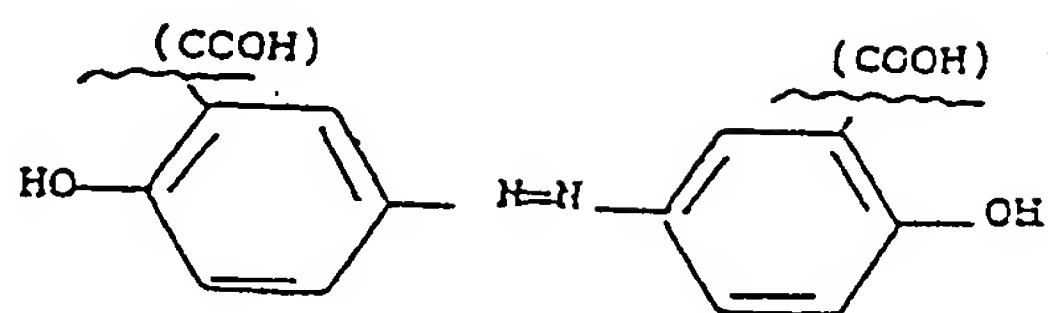
Ib)



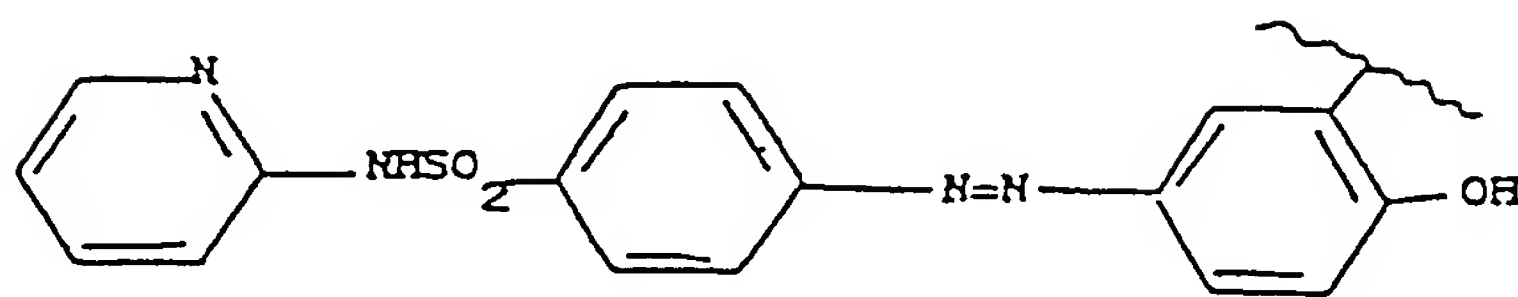
Ic)



IC₁)



IC₂)



IC₃)

wherein:

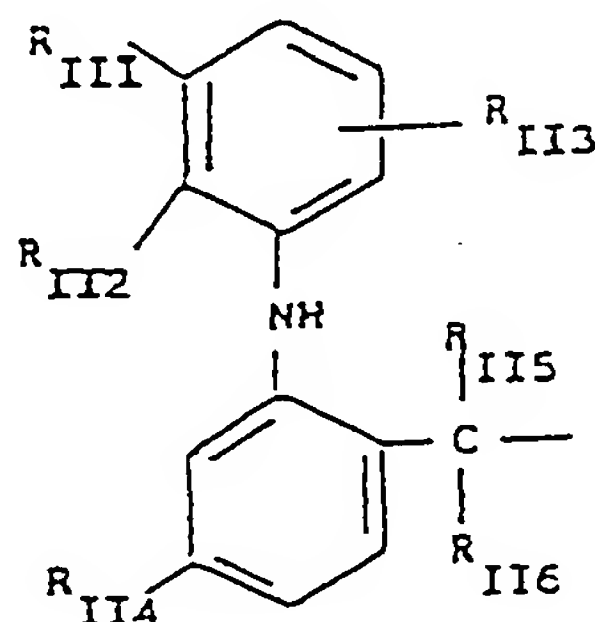
R_1 is the $OCOR_2$ group; wherein R_2 is methyl, ethyl or linear or branched C_1-C_5 alkyl, or the residue of a heterocycle with a single ring having 5 or 6 atoms which may be aromatic, partially or totally hydrogenated, containing one or more hetero-atoms independently selected from O, N and S;

R_2 is hydrogen, hydroxy, halogen, a linear or when possible branched C_1-C_4 alkyl, a linear or when possible branched C_1-C_4 alkoxyl; a linear or when possible branched C_1-C_4 perfluoroalkyl, for example trifluoromethyl; nitro, amino, mono- or di- (C_{1-4}) alkylamino;

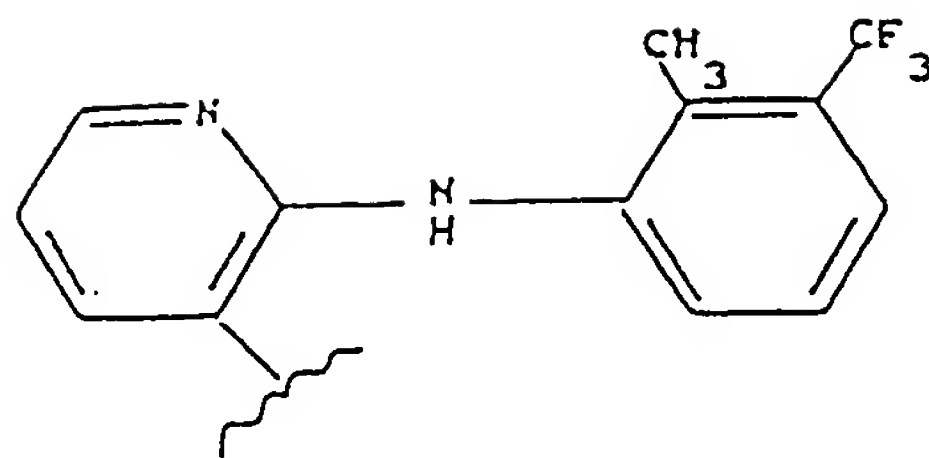
nI is an integer 0 or 1;

Group II) wherein $t = 1$, $u = 1$

IIa)



I Ib)



wherein:

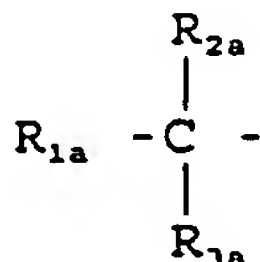
R_{II5} is H, a linear or when possible branched C_1 - C_3 alkyl;

R_{II6} has the same meaning as R_{II5} , or when R_{II5} is H it may be benzyl;

R_{III1} , R_{III2} and R_{III3} can independently be hydrogen, a linear or when possible branched C_1 - C_6 alkyl or a linear or when possible branched C_1 - C_6 alkoxy, or Cl, F, Br;

R_{III4} is R_{III1} or bromine;

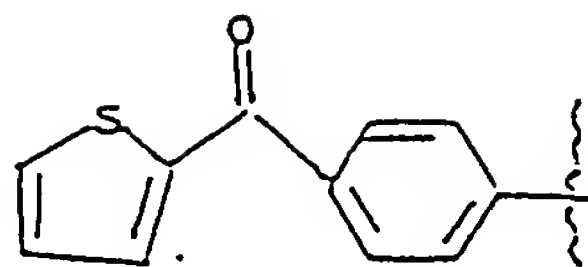
Group III) wherein $t = 1$, $u = 1$ and R is



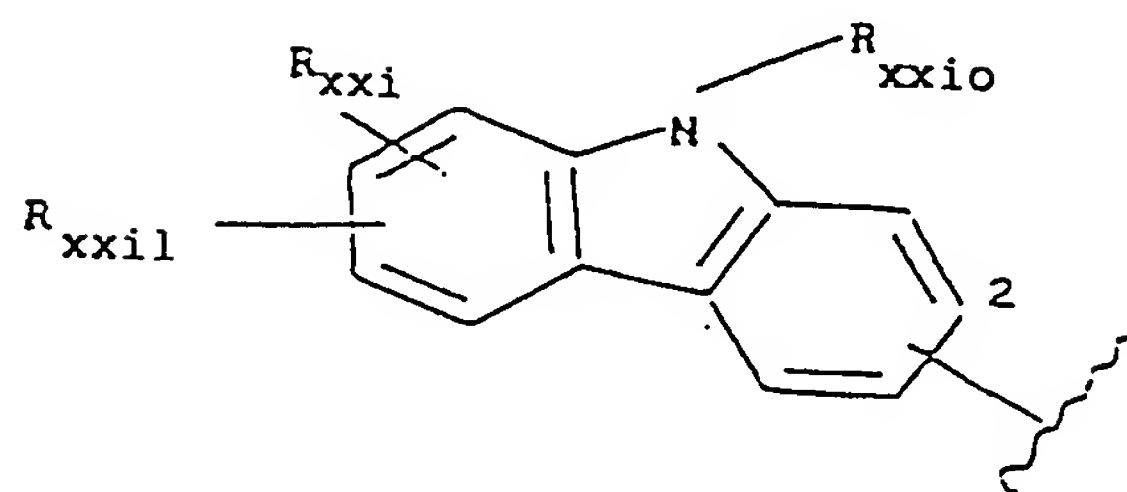
wherein:

R_{2a} and R_{3a} are H, a linear or when possible branched, substituted or non-substituted, C_1 - C_{12} alkyl or allyl, with the proviso that when one of the two is allyl, the other is H; preferably R_{2a} is H, C_1 - C_4 alkyl, R_{3a} is H;

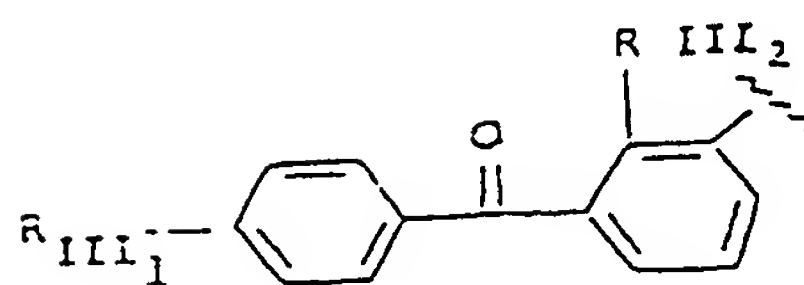
R_{1a} is selected from



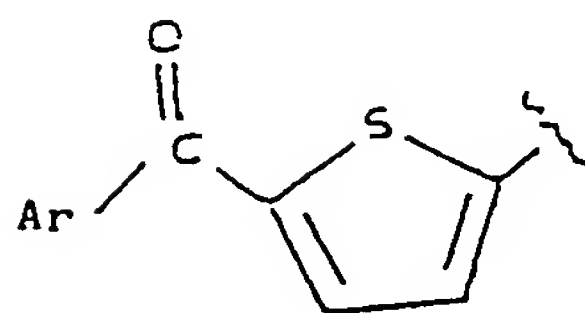
(II)



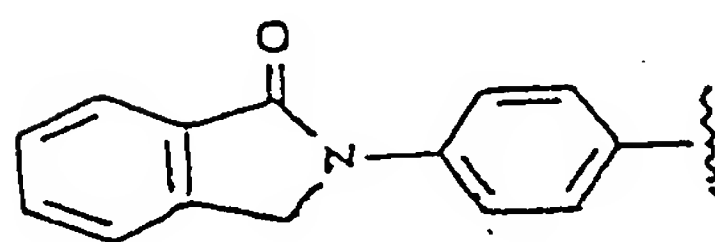
(XXI)



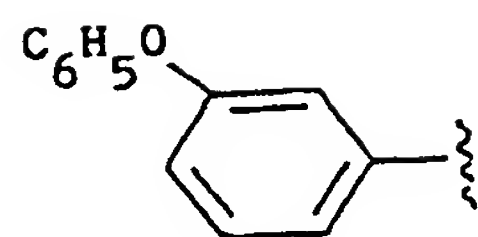
(IV)



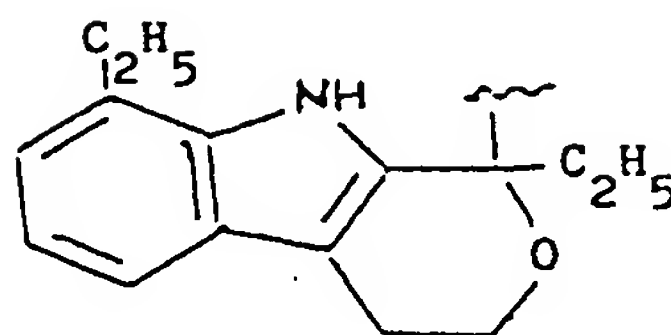
(XXXV)



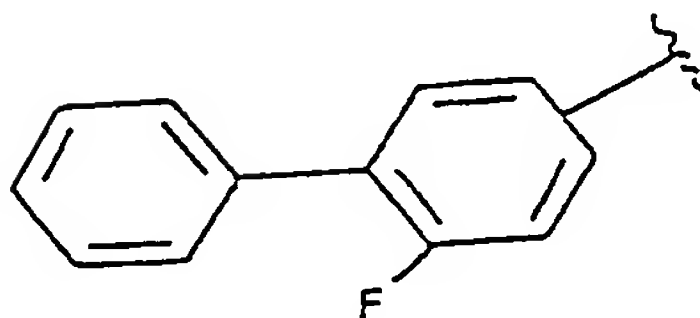
(VI)



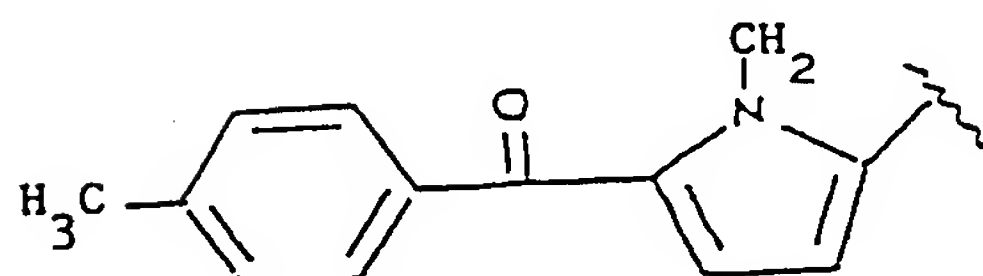
(VII)



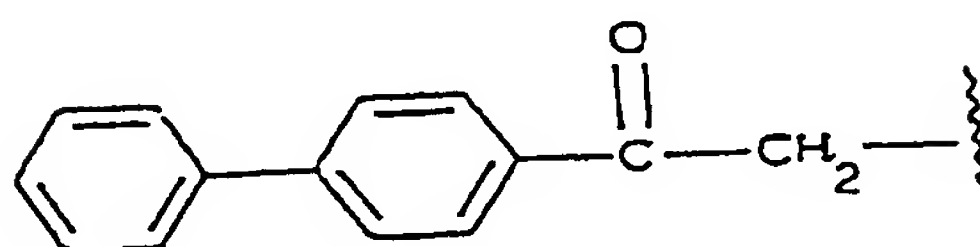
(VIII)



(IX)

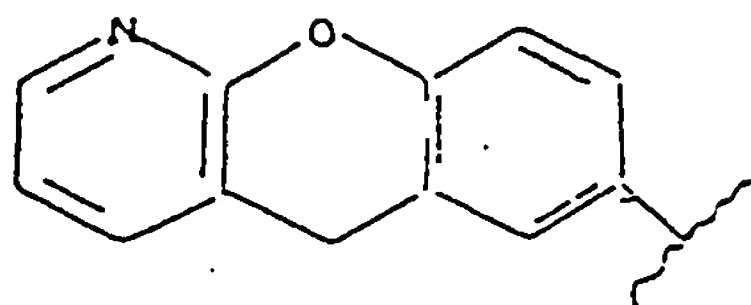


(X)

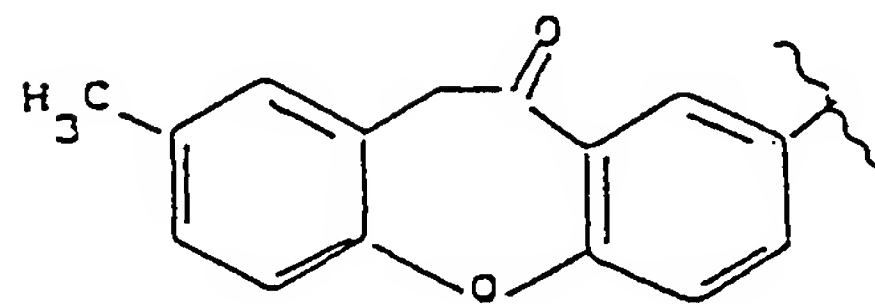


(III)

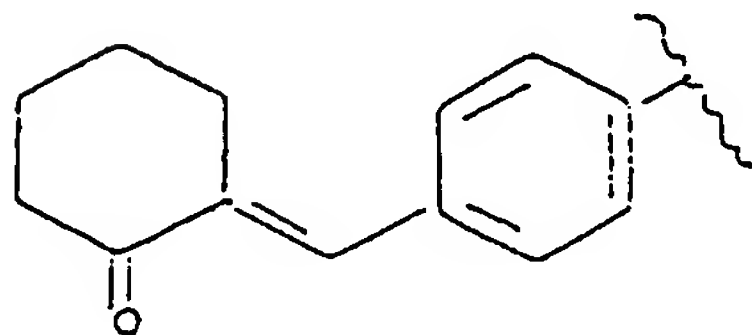
IIID) R_{1a} corresponds to the following formulas:



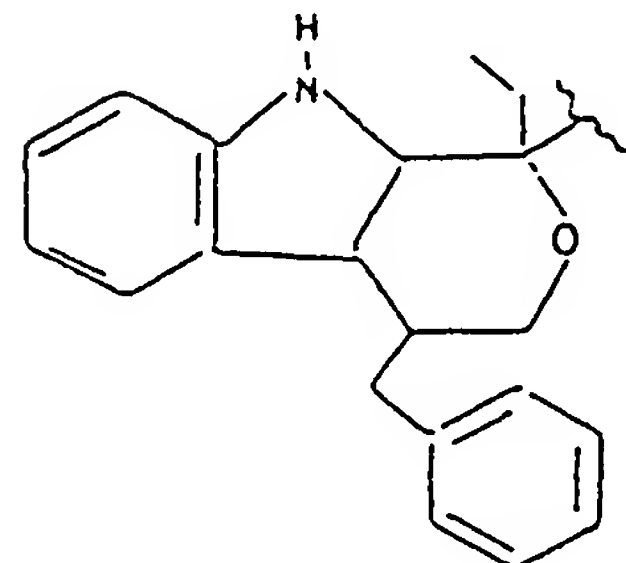
IIIa)



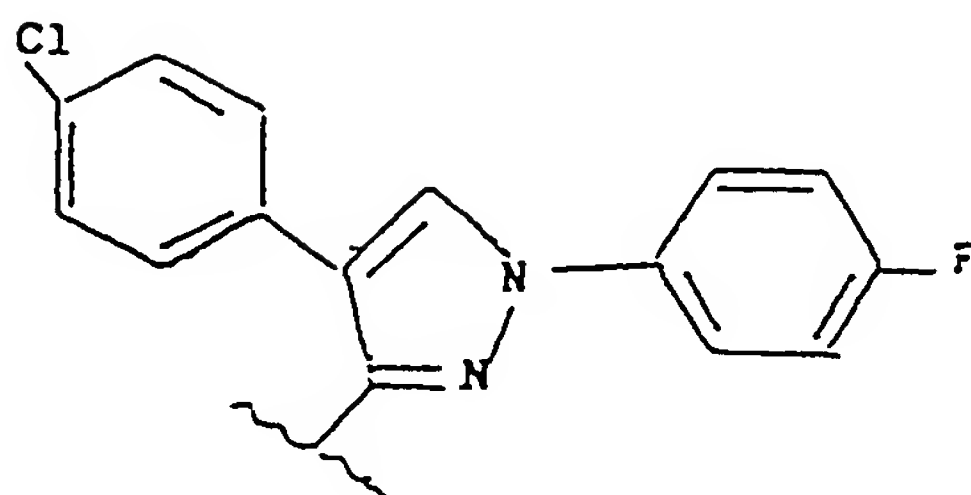
(xxx)



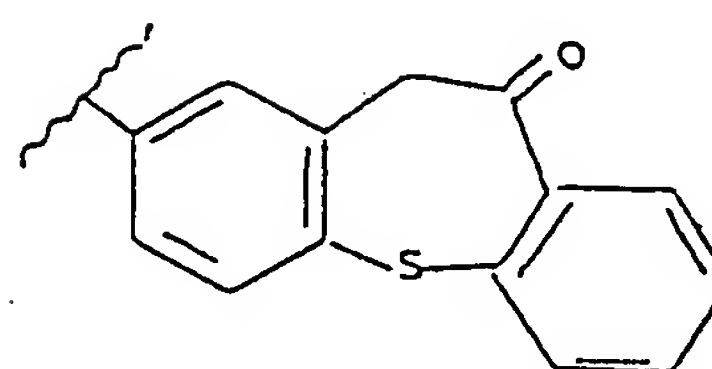
(xxxi)



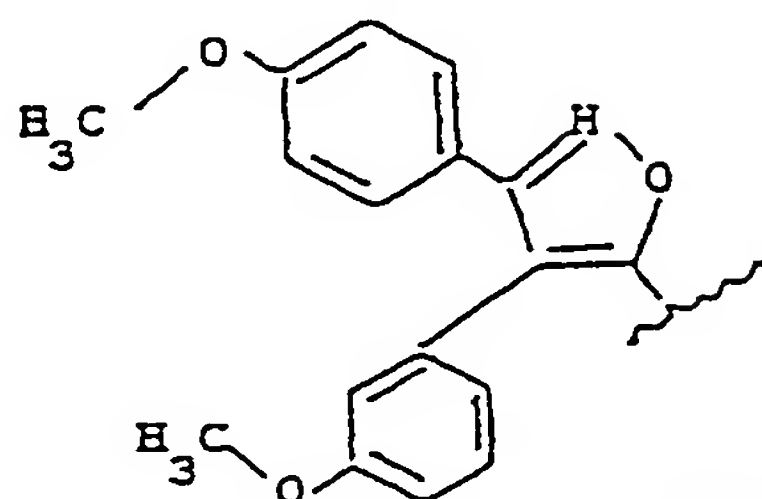
(xxxii)



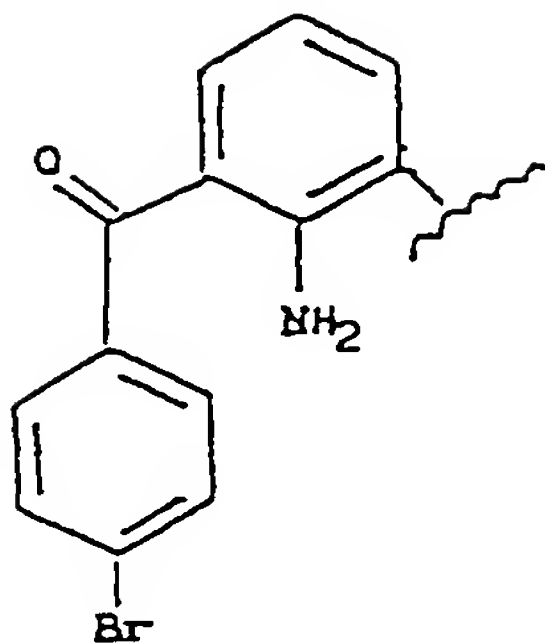
(xxlii)



(xxvi)



(xxvii)



(XII)

wherein the meanings are the following:

- when R_{1a} is as defined in formula (IV), Ketoprofen residue: R_{1111} is H, SR_{1112} wherein R_{1112} contains from 1 to 4 C atoms, linear or branched when possible; R_{1112} is H, hydroxy;
- when R_{1a} is as defined in formula (XXI), carprofen residue: R_{xx10} is H, a linear or when possible branched alkyl from 1 to 6 C atoms, a C_1 - C_6 alkoxy carbonyl bound to a C_1 - C_6 alkyl, C_1 - C_6 carboxyalkyl, C_1 - C_6 alkanoyl, optionally substituted with halogens, benzyl or halobenzyl, benzoyl or halobenzoyl;
 R_{xx1} is H, halogen, hydroxy, CN, C_1 - C_6 alkyl optionally containing OH groups, C_1 - C_6 alkoxy, acetyl, benzyloxy, SR_{xx12} wherein R_{xx12} is C_1 - C_6 alkyl; C_1 - C_3 perfluoroalkyl; C_1 - C_6 carboxyalkyl optionally containing OH groups, NO_2 , amino; sulphamoyl, di-alkyl sulphamoyl with C_1 - C_6 alkyl, or di-fluoroalkylsulphonyl with C_1 - C_3 alkyl;

R_{xxi1} is halogen, CN, C_1-C_6 alkyl containing one or more OH groups, C_1-C_6 alkoxy, acetyl, acetamido, benzyloxy, SR_{III} , being as above defined, C_1-C_6 perfluoroalkyl, hydroxy, C_1-C_6 carboxyalkyl, NO_2 , amino, mono- or di-alkyl-amino C_1-C_6 ; sulphamoyl, di-alkyl sulphamoyl C_1-C_6 , or di-fluoroalkylsulphamoyl as above defined; or R_{xxi} together with R_{xxi1} is a C_1-C_6 alkylene dioxy;

- when R_{1a} is as defined in the formula (XXXV), residue of the tiaprofenic acid:

Ar is phenyl, hydroxyphenyl optionally mono- or poly-substituted with halogen, C_1-C_6 alkanoyl and alkoxy, C_1-C_6 trialkyl, preferably C_1-C_3 , cyclopentyl, cyclohexyl cycloheptyl, heteroaryl, preferably thienyl, furyl optionally containing OH, pyridyl;

- when R_{1a} is as defined in formula (II), suprofen residue, wherein R_{3a} is H, R_{2a} is methyl and $X = O$;
- when R_{1a} is as defined in formula (VI), R is the residue of indoprofen when $R_{2a} = H$ and $R_{3a} = CH_3$ and of indobufen when R_{2a} is equal to H and $R_{3a} = C_2H_5$; $X = O$;
- when R_{1a} is as defined in formula (VIII), R is the residue of etodolac when $R_{2a} = R_{3a} = H$ and $X = O$;
- when R_{1a} is as defined in formula (VII), R is the residue of fenoprofen when $R_{3a} = H$, $R_{2a} = CH_3$ and

X = O;

- when R_{1a} is as defined in formula (III), R is the residue of fenbufen wherein $R_{2a} = R_{3a} = H$ and $X = O$;
- when R_{1a} is as defined in formula (IX), R is the residue of flurbiprofen when $R_{3a} = H$, $R_{2a} = CH_3$, $X = O$;
- in the compounds of formula (X) R is the residue of tolmetin when $R_{2a} = R_{3a} = H$, $X = O$;

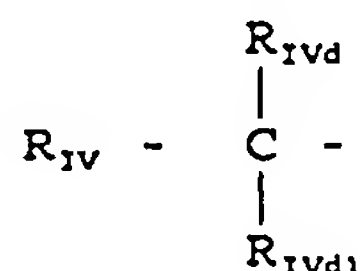
in the group IIID) R_{1a} corresponds to the following formulas:

- IIIa), when $R_{2a} = H$ and $R_{3a} = CH_3$, the residue of pranoprofen is obtained: α -methyl-5H-[1]benzopyran-[2,3-b]pyridin-7-acetic acid;
- (XXX), when $R_{2a} = H$ and $R_{3a} = CH_3$, the bermoprofen residue is obtained: dibenz[b,f]oxepin-2-acetic acid;
- (XXXI), when $R_{2a} = H$ and $R_{3a} = CH_3$, R is the radical of the compound CS-670: 2-[4-(2-oxo-1-cyclohexylidenemethyl) phenyl]propionic acid;
- (XXXII), when $R_{2a} = R_{3a} = H$ the Pemedolac residue is obtained;
- (XXXIII), when $R_{2a} = R_{3a} = H$ the pirazolac residue is obtained: 4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolic acid;
- (XXXVI), when $R_{2a} = H$, $R_{3a} = CH_3$, the zaltoprofen

residue is obtained; when the residue is saturated with an hydroxyl or aminic group or with the carboxylic function the compounds are known as dibenzothiepin derivatives;

- (XXXVII), when $R_{2a} = R_{3a} = H$ the mofezolac residue is obtained: 3,4-di(p-methoxyphenyl)isoxazol-5-acetic acid;
- (XII), when $R_{2a} = R_{3a} = H$ the bromfenac residue is obtained: 2-amino-3-(4-bromobenzoyl)benzeneacetic acid;

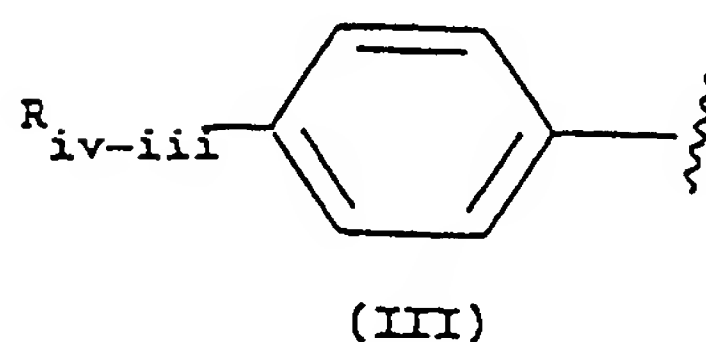
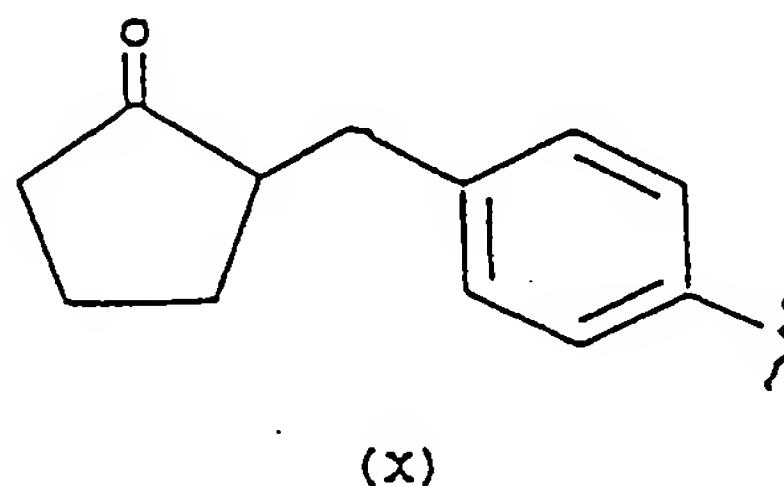
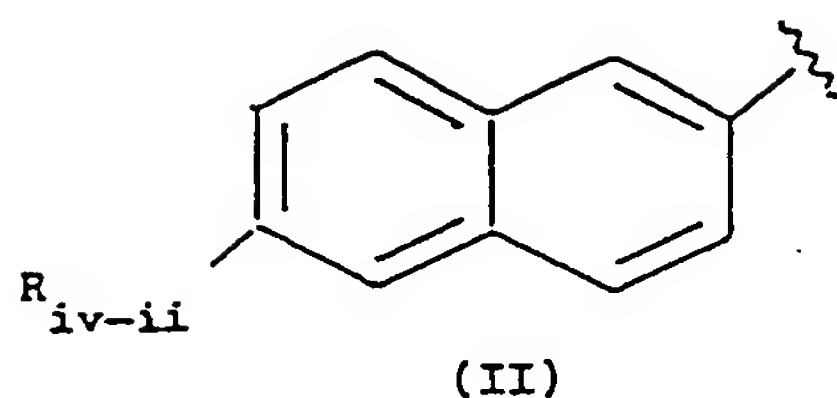
in group IV) wherein $t = 1$, $u = 1$, R is



wherein:

R_{IVd} and R_{IVd1} are at least one H and the other a linear or branched when possible alkyl from C_1 to C_6 , preferably C_1 and C_2 , or difluoroalkyl with the alkyl having from 1 to 6 C atoms, C_1 is preferred, or R_{IVd} and R_{IVd1} form together a methylene group;

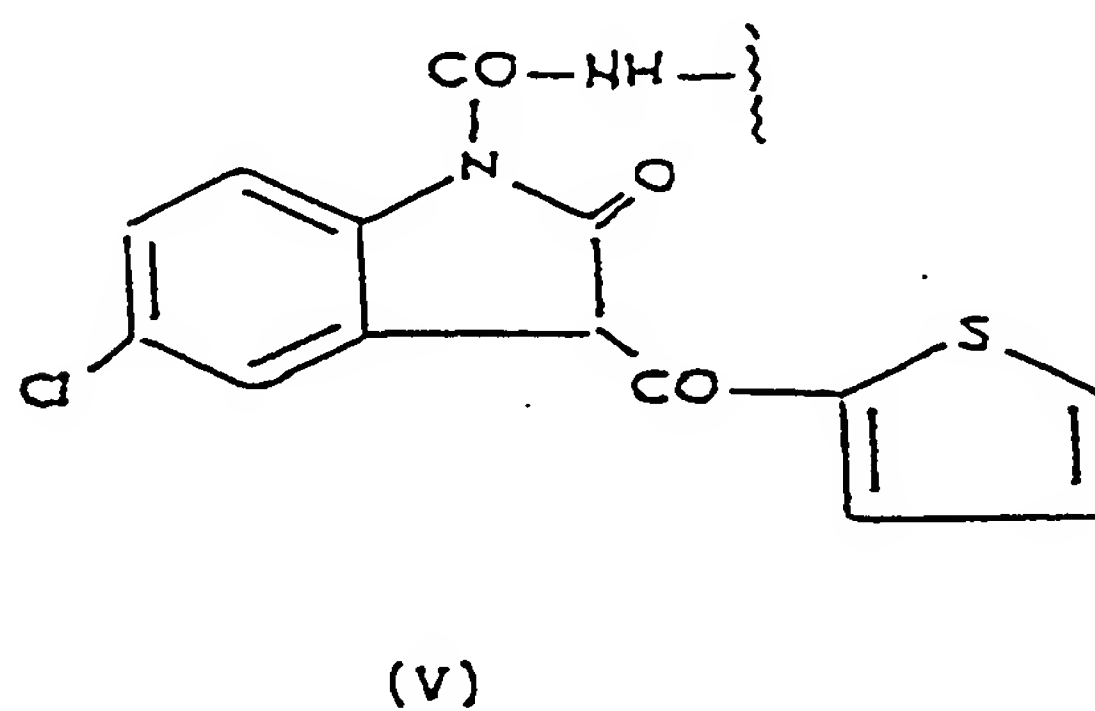
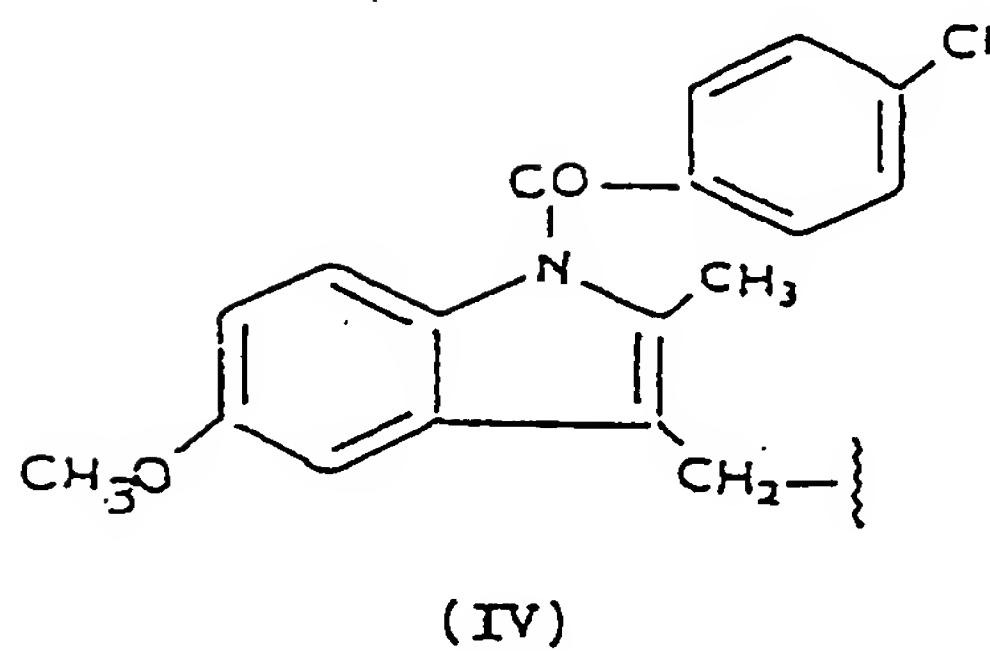
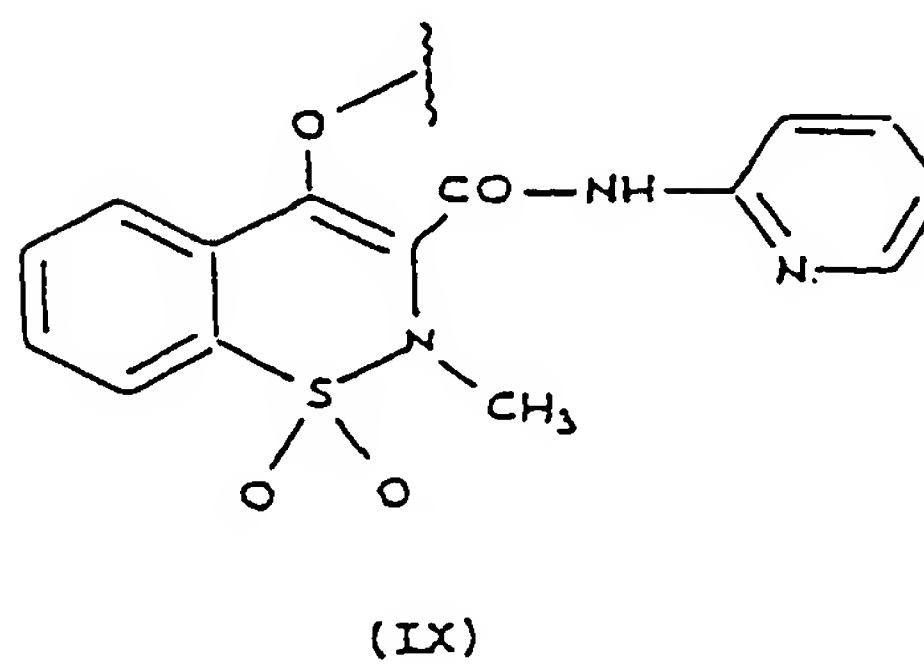
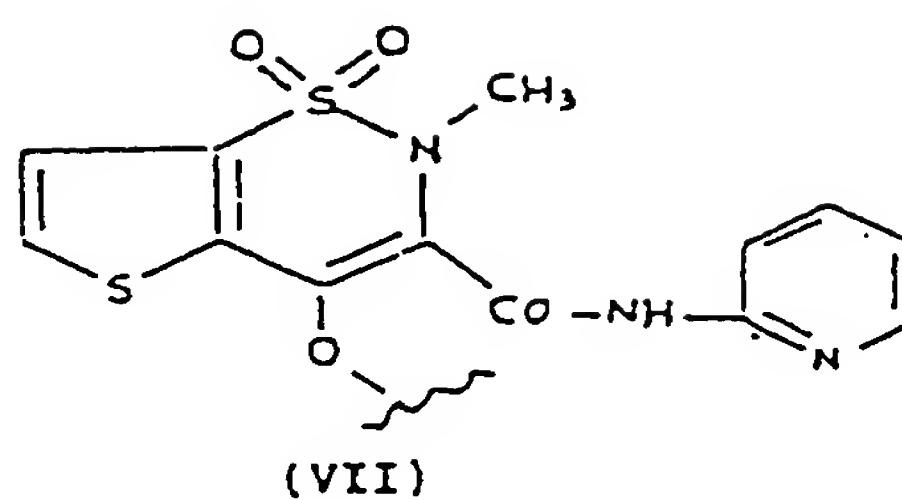
R_{IV} has the following meaning:

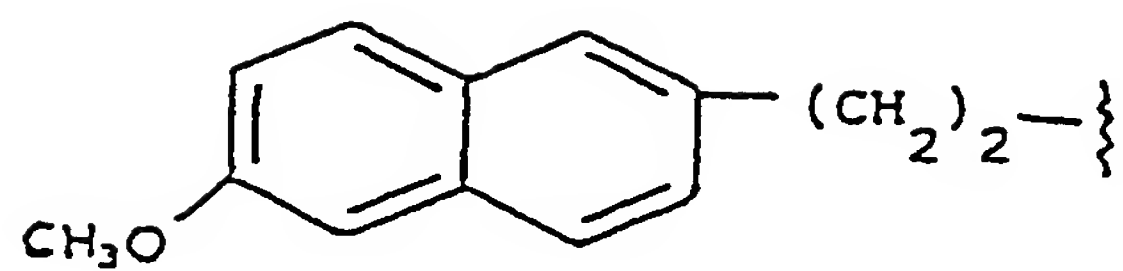


wherein:

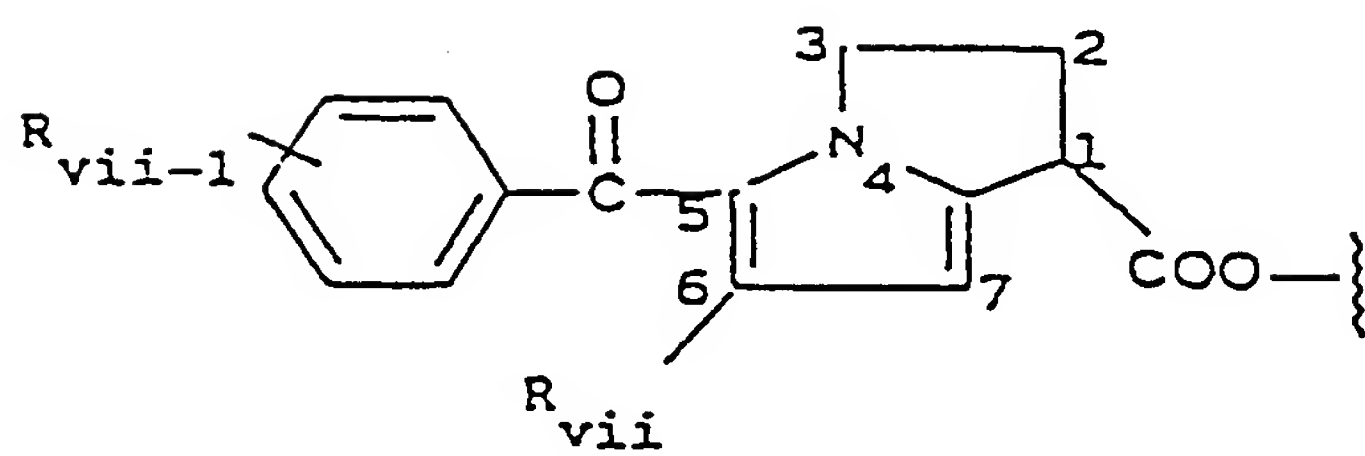
- in formula (II) R_{iv-ii} is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_7 alkoxyethyl, C_1-C_6 trifluoroalkyl, vinyl, ethynyl, halogen, C_1-C_6 alkoxy, difluoroalkoxy with the C_1-C_7 alkyl, C_1-C_7 alkoxyethoxy, alkylthiomethoxy with the C_1-C_7 alkyl, alkyl methylthio with the C_1-C_7 alkyl, cyano, difluoromethylthio, phenyl- or phenylalkyl substituted with the C_1-C_6 alkyl;
- formula (X), loxoprofen residue;
- in formula (III) R_{iv-iii} is a C_2-C_6 alkyl, optionally branched when possible, C_2 and C_3 alkyloxy, allyloxy, phenoxy, phenylthio, cycloalkyl having from 5 to 7 C atoms, optionally substituted in position 1 with a C_1-C_2 alkyl;

Group V)



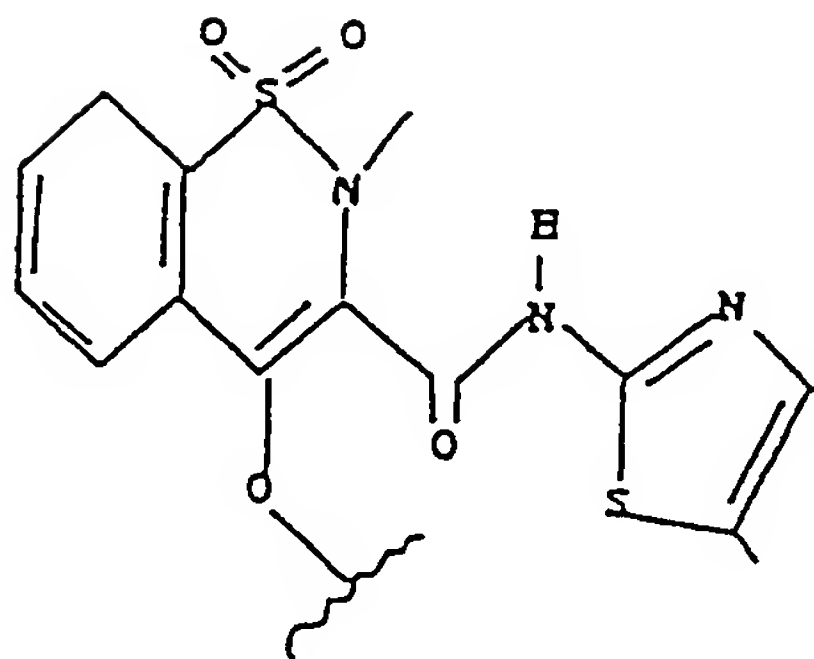


(III)

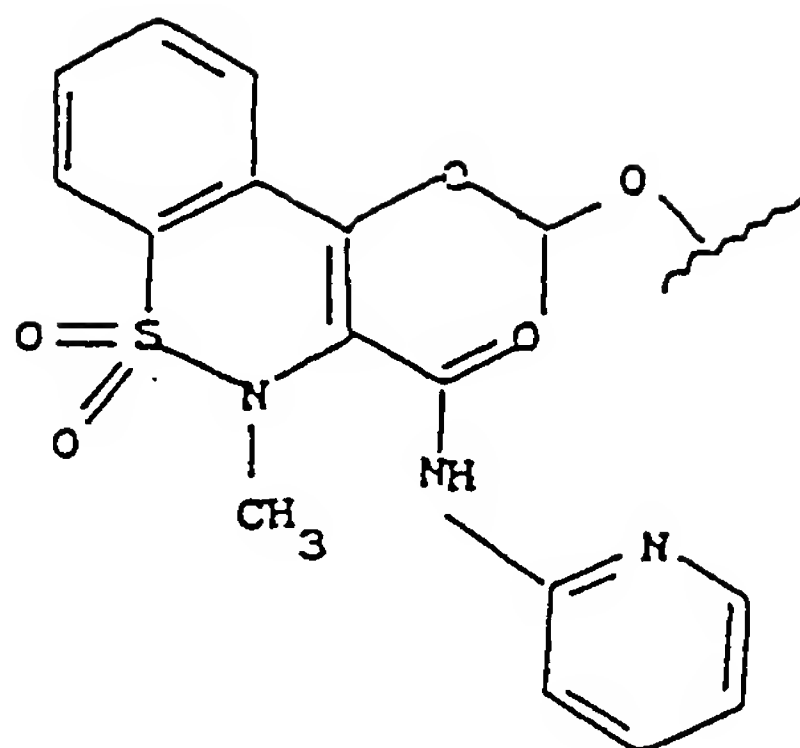


(II)

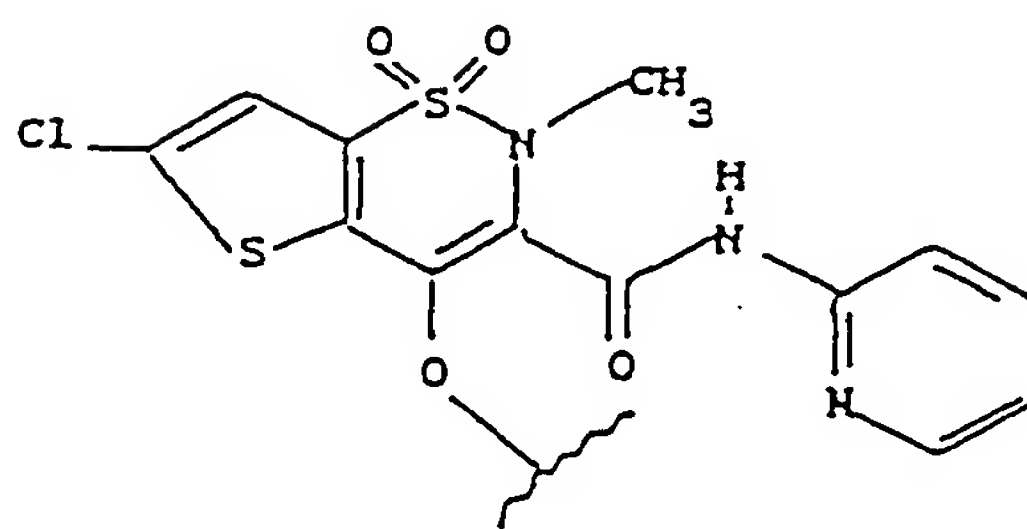
Group VE)



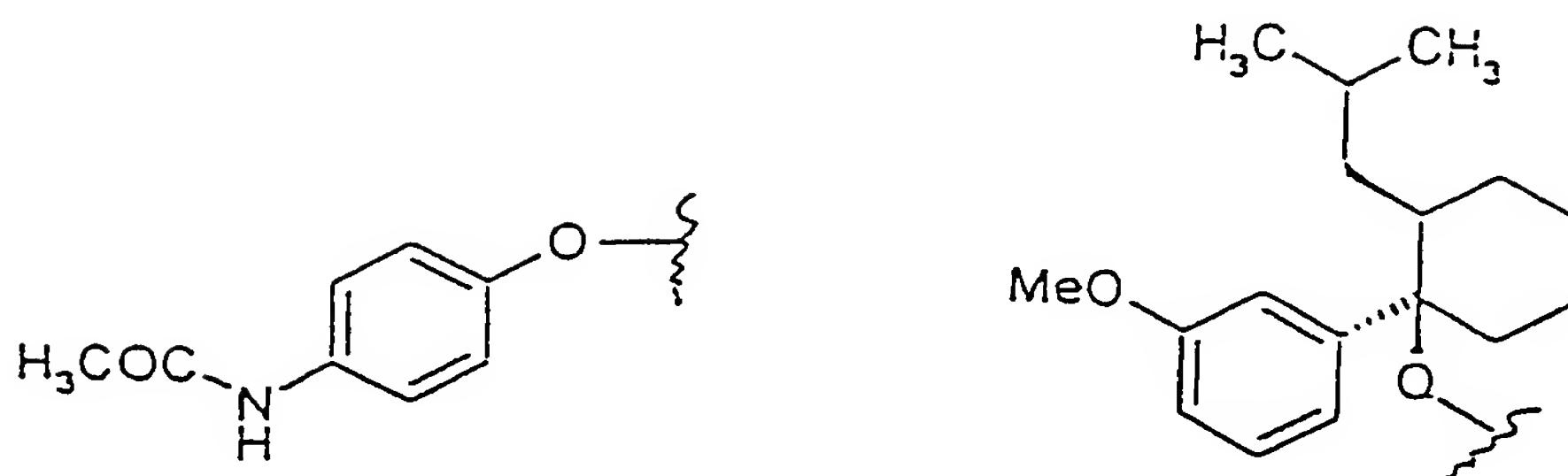
(x)



(XI)



(XIII)



(XXXX)

(XXXXI)

In group V),

- when R is the formula (II), R_{VII} is H or a linear or branched when possible C_1-C_4 alkyl;
 R_{VII-1} is R_{VII} , or a linear or branched when possible C_1-C_4 alkoxy; Cl, F, Br; the position of R_{VII-1} being ortho, or meta, or para;
- when R is the formula (V), $A = R$ and $t = 0$;
- when R is the formula (VII), A is RCO, $t = 1$ $u = 0$ or A is R and $t = 0$;
- when R is the formula (IX), $A = R$ and $t = 0$, or A = RCO with $t = 1$ and $u = 0$;
- when R is the formula (III) $A = RCOO$, $t = 1$ and $u = 0$ or 1; or $t = 0$ and $A = R$;
- when R is the formula (IV), $A = RCOO$, $t = 1$ and $u = 1$;
- when R is the formula (X), it is the residue of meloxicam;
- when R is constituted of the formula (XI), it is known as ampiroxicam when the end group is $-CH(CH_3)OCOC_2H_5$;
- when R is the formula (XIII) and the free valence is saturated with H, the residue is that of lornoxicam;
- when R is the formula (XXXX) and the valence is saturated with H, the compound is known as paracetamol;

- when R is the formula (XXXXI) and the valence is saturated with H, the residue is known as tramadol.
2. Salts according to claim 1, wherein in the compounds of formula $A-X_1-N(O)_z$, z is 2 and n_{IX} and n_{IIX} in the formula (B) of X_1 are integers equal to 1 and R_{TIX} , $R_{TIX'}$, R_{TIIIX} , $R_{TIIIX'}$ are equal to H.
3. Salts according to claims 1 and 2, wherein in the compounds of formula $A-X_1-N(O)_z$, R, X , u and t of the formula $A = R(COX_u)_t$, and Y in formula (B) of X_1 , have the following meanings:

when R is selected from Group I),

- in the compounds of formula Ia) X is equal to O or NH, R_1 is acetoxy, preferably in ortho-position with respect to $-CO-$, R_2 is hydrogen; in X_1 $R_{TIX} = R_{TIX'} = R_{TIIIX} = R_{TIIIX'} = H$, $n_{IX} = n_{IIX} = 1$ and Y is an aromatic ring having 6 atoms, containing a nitrogen atom, said aromatic ring having the two free valences in position 2 and 6;
- in the compounds of formula Ib) $R_3 = CH_3$, $n_I = 0$, X is equal to O, X_1 is as above defined for Ia); in this case Ib) is the residue of the acetylsalicylsalicylic acid;
- in the compounds of formula Ic) $X = O$ and $u = 1$;

when R is selected from Group II),

- in the formula IIa R_{III1} , R_{III4} are hydrogen and R_{III2} and

R_{III} are chlorine in ortho-position with respect to NH; R_{III5} and R_{III6} are H, X is equal to O, and X_1 is as above defined for the compounds of formula Ia);

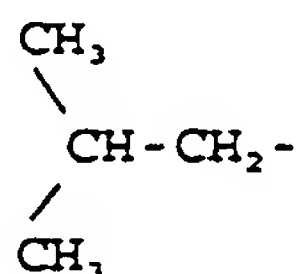
when R is selected from Group III),

- when R_{1a} is as defined in formula (IV), R_{III1} and R_{III2} are H, R_{3a} is H, and R_{2a} is methyl, $X = O$;
- when R_{1a} is as defined in formula (XXI), R_{xx10} is H, the linking bridge is in position 2, R_{xx1} is H, R_{xx11} is chlorine and is in para position with respect to nitrogen;
- when R_{1a} is as defined in the formula (XXXV), Ar is phenyl, R_{3a} is H, R_{2a} is methyl and X is O; R_{3a} is H, R_{2a} is methyl and X is O;
- when R_{1a} is as defined in the formula IIIa), $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$;
- when R_{1a} is as defined in the formula (XXX) $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$;
- when R_{1a} is as defined in the formula (XXXI), $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$;
- when R_{1a} is as defined in the formula (XXXII), $R_{2a} = R_{3a} = H$, $u = 1$ and $X = O$;
- when R_{1a} is as defined in the formula (XXXIII), $R_{2a} = R_{3a} = H$, $u = 1$ and $X = O$;
- when R_{1a} is as defined in the formula (XXXVI), $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$;

- when R_{1a} is as defined in the formula (XXXVII), R_{2a}
 $= R_{3a} = H$, $t = 1$ and $X = O$;
- when R_{1a} is as defined in the formula (XII), $R_{2a} = R_{3a}$
 $= H$, $u = 1$, $t = 1$, $X = O$, $R_{2a} = R_{3a} = H$; or $t = 0$

when R is selected from Group IV),

- when R_{IV} is the formula (II), $R_{iv-ii} = CH_3O-$, $R_{IVd} = H$
and $R_{IVd1} = CH_3$, $X = O$ and X_1 is as above defined for
Ia);
- when R_{IV} is the formula (X), $R_{IVd} = H$, $R_{IVd1} = CH_3$,
 $X = O$ and X_1 is as above defined for Ia);
- when R_{IV} is the formula (III), R_{iv-iii} is



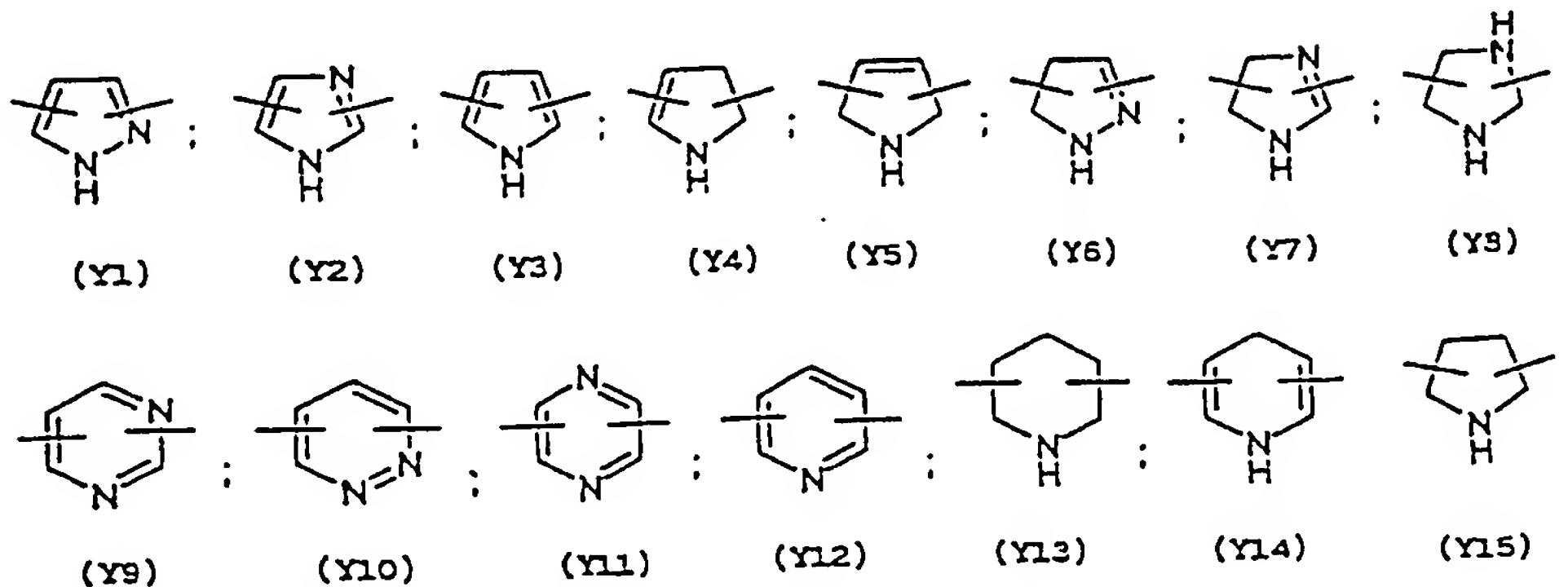
and $R_{IVd} = H$, R_{IVd1} is CH_3 , $X = O$ and X_1 is as above
defined for Ia);

when R is selected from Group V,

- when R is the formula (II), R_{vii} and R_{vii-1} are H ,
and $A = R$;
- when R is the formula (X), $A = RCO$, $t = 1$ and $u = 0$;
- when R is the formula (XI), $A = RCO$,
 $t = 1$ and $u = 0$;
- when R is the formula (XIII), $A = RCO$, $t = 1$ and
 $u = 0$;
- when R corresponds to the formula (XXXX) or (XXXXI),

$A = RCO$, $t = 1$ and $u = 0$.

4. Salts according to claims 1-3, wherein Y in formula (B) of X_1 contains one or two nitrogen atoms in the ring and is selected from the following:



5. Salts according to claim 4, wherein the preferred radical Y of formula (B) of X_1 is Y12 (pyridyl) substituted in position 2 and 6.
6. Salts according to claims 1-5, wherein the organic acids are selected from the following: oxalic, tartaric, maleic, succinic, citric acids and the inorganic acids from nitric, hydrochloric, sulphoric, phosphoric acids.
7. Salts according to claims 1-6, wherein R in formula A = $R(COX_u)_t$ is selected among those of Group I) and Group IV).
8. Salts according to claims 1-7 for use as medicaments.
9. Use of salts according to claim 8 for the preparation of drugs having an antiinflammatory activity.

10. Use of salts according to claim 8 for the preparation of drugs for the antithrombotic therapy.
11. Use of salts according to claim 8 for the preparation of drugs having an analgesic activity.
12. Use of salts according to claim 8 for the preparation of drugs for the septic shock therapy.
13. Pharmaceutical formulations for oral and parenteral use containing as active principles the salts of claims 1-7.
14. Compounds of formula



according to claims 1-8.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/01454

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D213/30 C07D401/12 A61K31/44 A61P29/00 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 30641 A (NICOX LTD ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 16 November 1995 (1995-11-16) cited in the application page 59 -page 77; claim 1 page 45 -page 49; example 1C ---	1-14
A	WO 97 16405 A (NICOX SA ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 9 May 1997 (1997-05-09) cited in the application page 12 -page 15; example 3 -----	1-14

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

6 June 2000

Date of mailing of the international search report

19. 06. 00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fink, D

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/01454

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-4 (partly), 6-14 (partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4 (partly), 6-14 (partly)

Present claims 1 and 14 relate to an extremely large number of possible compounds/salts. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/salts claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds/salts of the present general formula wherein Y represents a 2,6-pyridindiy1, i.e., to the compounds/salts as defined by the present claim 5.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/01454

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/00		A2	(11) International Publication Number: WO 00/54756 (43) International Publication Date: 21 September 2000 (21.09.00)
(21) International Application Number: PCT/CA00/00280 (22) International Filing Date: 15 March 2000 (15.03.00) (30) Priority Data: 09/267,379 15 March 1999 (15.03.99) US (71) Applicant: QUEEN'S UNIVERSITY AT KINGSTON [CA/CA]; Kingston, Ontario K7L 3N6 (CA). (72) Inventors: THATCHER, Gregory, R., J. ; 116 Toronto Street, Kingston, Ontario K7L 4A7 (CA). BENNETT, Brian, M. ; 36 Fairway Hills Crescent, Kingston, Ontario K7M 2B4 (CA). REYNOLDS, James, N. ; 52 Herchmer Crescent, Kingston, Ontario K7M 2V9 (CA). BOEGMAN, Roland, J. ; 320 Willingdon Avenue, Kingston, Ontario K7L 4J4 (CA). JHAMANDAS, Khem ; 17 Jorene Drive, Kingston, Ontario K7M 3X5 (CA). (74) Agents: SCRIBNER, Stephen, J. et al. ; Parteq Innovations, Queen's University at Kingston, Kingston, Ontario K7L 3N6 (CA).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(54) Title: NITRATE ESTERS AND THEIR USE FOR NEUROLOGICAL CONDITIONS			
(57) Abstract Compounds and methods for mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement in a subject are described. Neurological or cognitive conditions are treated by administering to a subject an effective amount of a therapeutic compound comprising a nitrate ester, or a pharmaceutically acceptable salt or ester thereof.			

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NITRATE ESTERS AND THEIR USE FOR NEUROLOGICAL CONDITIONS

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FIELD OF THE INVENTION

This invention relates to nitrate esters and use thereof in effecting neuroprotection, mitigating neurodegeneration and/or effecting cognition enhancement. More particularly, this invention relates to organic nitrates having therapeutic utility as neuroprotective agents and/or cognition enhancers. The invention still more particularly relates to nitrate esters bearing a sulfur or phosphorus atom β or γ to a nitrate group and their congeners which have therapeutic utility as neuroprotective agents and/or cognition enhancers.

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BACKGROUND OF INVENTION

The nitrate ester glyceryl trinitrate (GTN) or nitroglycerin, has been used as a vasodilator in the treatment of angina pectoris for over a hundred years, and the dominant contemporary belief is that GTN exerts its therapeutic effect through *in vivo* release of nitric oxide (NO). Other organic nitrates, such as isosorbide dinitrate, have also been identified as effective and clinically important vasodilators. NO itself has been identified as Endothelium Derived Relaxing Factor (EDRF) and several classes of compounds, for example nitrosothiols, in addition to organic nitrates, have been proposed as NO donors or NO prodrugs. Well-known examples of these classes of compound and one nitrate, GTN itself, have been suggested to demonstrate neurotoxic or neuroprotective effects by dint of interactions with the redox modulatory site of the *N*-methyl-D-aspartate (NMDA) excitatory amino acid receptor. Thus GTN is firstly a potent vasodilator and secondly possesses

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potential neuroprotective properties. Several attempts have been made to increase the efficacy or potency of alternative organic nitrates as vasodilators relative to GTN, for example, by incorporation of propanolamine or cysteine functionalities. However, no attempt has been made to separately regulate the vasodilatory and neuroprotective effects of GTN. Indeed, postural hypotension, weakness and other signs of cerebral ischemia are adverse effects, associated with the vasodilatory effects of GTN and observed in treatment, which are highly contraindicated of GTN itself, and by extrapolation GTN derivatives (1,2,3-trinitratopropane derivatives), as clinically useful neuroprotective therapeutic agents.

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OBJECTS AND SUMMARY OF THE INVENTION

In as much as the potent vasodilatory effects of organic nitrates may prove (a) deleterious to, or alternatively (b) synergistic with the neuroprotective effects of GTN, it is postulated herein that regulation of these two effects is required for development of new and useful neuroprotective therapeutic agents. Further, it is postulated that such regulation may be achieved through use of an appropriate organic nitrate, such as, for example, nitrate esters incorporating sulfur-containing or phosphorus-containing functionalities into the structure of the nitrate esters or through use of their congeners. Interaction of organic nitrates with amino acid neurotransmitter receptors, including the NMDA receptor, will provide examples of compounds with neuroprotective properties, but modulation of the γ -aminobutyric acid type A (GABA_A) receptor response will provide examples of organic nitrates capable of cognition enhancement. Stimulation of cerebral soluble guanylyl cyclase (GCase) by organic nitrates, in particular selectively over arterial GCase, will provide examples of compounds with neuroprotective properties. Organic nitrates bearing antioxidant functionalities and those capable of inhibiting apoptosis will also provide examples of compounds with neuroprotective properties. These postulates are based, in part, on bioassay data on such compounds. Thus, there is a need for synthetic organic nitrates, such as, for example, nitrate esters containing sulfur or phosphorus functionalities or their congeners, as new and useful therapeutic agents for use in effecting neuroprotection, mitigating neurodegeneration and/or effecting cognition enhancement. It will be appreciated, therefore, that these compounds can be used for

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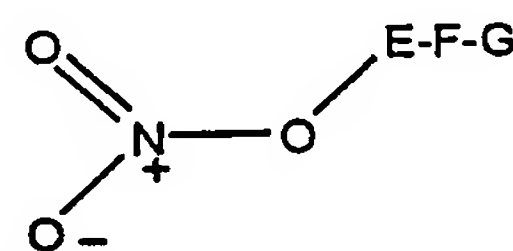
treatment conditions including but not limited to: stroke; Parkinson's disease; Alzheimer's disease; Huntington's disease; multiple sclerosis; amyotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism; alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma to the head; hypoglycemia; hypoxia; myocardial infarction; cerebral vascular occlusion; cerebral vascular hemorrhage; hemorrhage; environmental excitotoxins of plant, animal and marine origin; dementias of all type, trauma, drug-induced brain damage, aging.

It is an object of the present invention to provide novel organic nitrates, including aliphatic nitrate esters bearing a sulfur or phosphorus moiety β or γ to a nitrate group, or congeners thereof. Another object of the present invention is to provide methods for making such novel organic nitrates. Another object of the invention is to provide methods for effecting neuroprotection, mitigating neurodegeneration and /or effecting cognition enhancement employing organic nitrates. Another object of the present invention is to provide novel drugs as neuroprotective agents. Yet another object of the present invention is to provide novel drugs for use in cognition enhancement.

This invention provides novel compounds, methods and pharmaceutical compositions which are useful in the treatment of neurological disorders requiring mitigation of neurodegeneration, neuroprotection and/or cognition enhancement. Methods of the invention involve administering to a subject in need thereof a therapeutic compound which provides neuroprotection or cognition enhancement. Accordingly, the compositions and methods of the invention are useful for effecting neuroprotection or cognition enhancement in disorders in which neurotoxic damage occurs. The methods of the invention can be used therapeutically to treat conditions including but not limited to: stroke; Parkinson's disease; Alzheimer's disease; Huntington's disease; multiple sclerosis; amyotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism; alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma to the head; hypoglycemia; hypoxia; myocardial infarction; cerebral vascular occlusion; cerebral vascular hemorrhage; hemorrhage;

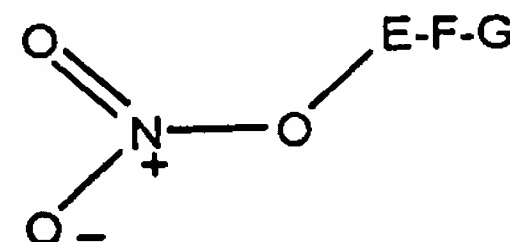
environmental excitotoxins; dementias of all type, trauma, drug-induced brain damage, and aging or can be used prophylactically in a subject susceptible or predisposed to these conditions. In certain embodiments, a therapeutic compound used in the method of the invention preferably can interact with GCase effecting neuroprotection and/or cognition enhancement. In other embodiments, a therapeutic compound used in the method of the invention preferably can modulate glutamate and/or non-glutamate neuroreceptor interactions effecting neuroprotection and/or cognition enhancement.

The invention relates to organic nitrates, i.e., nitrate esters. In one aspect, the invention provides a method including the step of administering to a subject an effective amount of a therapeutic compound having the formula (Formula I):



wherein E, F, G are organic radicals which may contain inorganic counterions, such that neurodegeneration is mitigated in the subject.

In another aspect, the invention provides a method including the step of administering to a subject an effective amount of a therapeutic compound having the

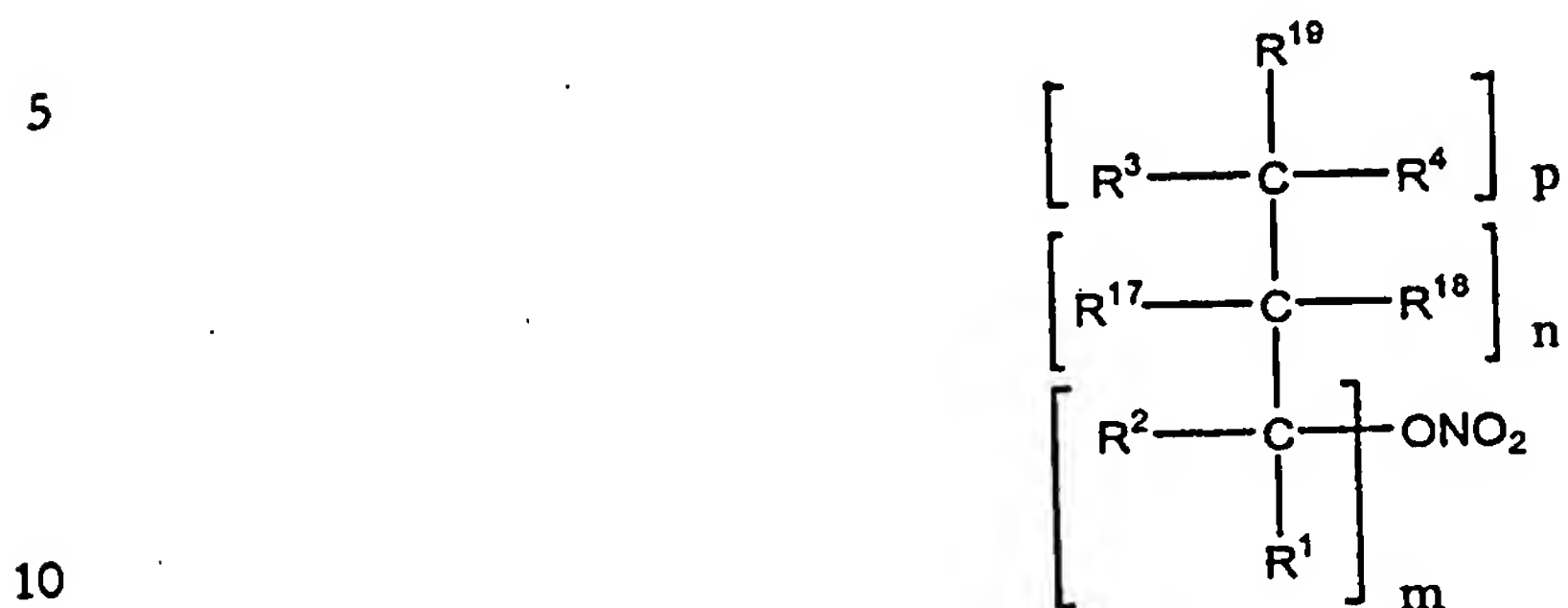


formula (Formula I):

wherein E, F, G are organic radicals which may contain inorganic counterions, such that cognition enhancement is effected.

In a further aspect, the invention provides use of therapeutic compounds that mitigate neurodegeneration, effect neuroprotection and/or effect cognition enhancement in a subject to

which the therapeutic compound is administered, the compounds having the formula (Formula II):



in which: m and n and p are integers from 0 to 10;

$R^{3,17}$ are each independently hydrogen, a nitrate group, or A;

$R^{1,4}$ are each independently hydrogen or A;

15 where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the

20 aliphatic ring, which optionally contains O, S, NR^6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, or amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R^1 and R^3 and/or between R^{17} and R^4 , which optionally contains O, S, NR^6 and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate,

25 amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. $\text{C}=\text{O}$, $\text{C}=\text{S}$, $\text{C}=\text{NOH}$), which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted

30 aryl group; a heterocyclic group; amino (including alkylamino,

dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylaryl amino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R^2, R^5, R^{18}, R^{19} are optionally hydrogen, A, or X-Y;

- 5 where X is F, Br, Cl, NO_2 , CH_2 , CF_2 , O, NH, NMe, CN, NHOH, N_2H_3 , $\text{N}_2\text{H}_2\text{R}^{13}$, $\text{N}_2\text{HR}^{13}\text{R}^{14}$, N_3 , S, SCN, $\text{SCN}_2\text{H}_2(\text{R}^{15})_2$, $\text{SCN}_2\text{H}_3(\text{R}^{15})$, $\text{SC}(\text{O})\text{N}(\text{R}^{15})_2$, $\text{SC}(\text{O})\text{NHR}^{15}$, SO_3M , SH, SR^7 , SO_2M , $\text{S}(\text{O})\text{R}^8$, $\text{S}(\text{O})_2\text{R}^9$, $\text{S}(\text{O})\text{OR}^8$, $\text{S}(\text{O})_2\text{OR}^9$, PO_2HM , PO_3HM , PO_3M_2 , $\text{P}(\text{O})(\text{OR}^{15})(\text{OR}^{16})$, $\text{P}(\text{O})(\text{OR}^{16})(\text{OM})$, $\text{P}(\text{O})(\text{R}^{15})(\text{OR}^8)$, $\text{P}(\text{O})(\text{OM})\text{R}^{15}$, CO_2M , CO_2H , CO_2R^{11} , $\text{C}(\text{O})$, $\text{C}(\text{O})\text{R}^{12}$, $\text{C}(\text{O})(\text{OR}^{13})$, PO_2H , PO_2M , $\text{P}(\text{O})(\text{OR}^{14})$,
 10 $\text{P}(\text{O})(\text{R}^{13})$, SO, SO_2 , $\text{C}(\text{O})(\text{SR}^{13})$, SR^5 , SSR^7 or SSR^5 ;

- Y is F, Br, Cl, CH_3 , CF_2H , CF_3 , OH, NH_2 , NHR^6 , NR^6R^7 , CN, NHOH, N_2H_3 , $\text{N}_2\text{H}_2\text{R}^{13}$, $\text{N}_2\text{HR}^{13}\text{R}^{14}$, N_3 , S, SCN, $\text{SCN}_2\text{H}_2(\text{R}^{15})_2$, $\text{SCN}_2\text{H}_3(\text{R}^{15})$, $\text{SC}(\text{O})\text{N}(\text{R}^{15})_2$, $\text{SC}(\text{O})\text{NHR}^{15}$, SO_3M , SH, SR^7 , SO_2M , $\text{S}(\text{O})\text{R}^8$, $\text{S}(\text{O})_2\text{R}^9$, $\text{S}(\text{O})\text{OR}^8$, $\text{S}(\text{O})_2\text{OR}^9$, PO_2HM , PO_3M_2 , $\text{P}(\text{O})(\text{OR}^{15})(\text{OR}^{16})$, $\text{P}(\text{O})(\text{OR}^{16})(\text{OM})$, $\text{P}(\text{O})(\text{R}^{15})(\text{OR}^8)$, $\text{P}(\text{O})(\text{OM})\text{R}^{15}$, CO_2M ,
 15 CO_2H , CO_2R^{11} , $\text{C}(\text{O})\text{R}^{12}$, $\text{C}(\text{O})(\text{OR}^{13})$, $\text{C}(\text{O})(\text{SR}^{13})$, SR^5 , SSR^7 or SSR^5 , or does not exist;

$R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents; or $\text{C}_1 - \text{C}_6$ connections to $\text{R}^1 - \text{R}^4$ in cyclic derivatives, or are each independently hydrogen, a nitrate group, or W;

- 20 M is H, Na^+ , K^+ , NH_4^+ , $\text{N}^+\text{H}_k\text{R}^{11}_{(4-k)}$ where k is 0-3, or other pharmaceutically acceptable counterion;

and with the proviso that, when $m = n = p = 1$; $\text{R}^{19}, \text{R}^2, \text{R}^{18}, \text{R}^1 = \text{H}$; $\text{R}^{17}, \text{R}^3$ are nitrate groups; that R^4 is not H or $\text{C}_1 - \text{C}_3$ alkyl.

- 25 Preferred therapeutic compounds for use in the invention include compounds in which R^{19} is X-Y. In some preferred embodiments: R^{19} is X-Y and $\text{R}^5, \text{R}^6, \text{R}^8, \text{R}^9, \text{R}^{10}, \text{R}^{12}, \text{R}^{13}, \text{R}^{14}, \text{R}^{15}, \text{R}^{16}$ are the same or different alkyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents, or C_1 or C_2 connections to $\text{R}^1 - \text{R}^3$ in cyclic derivatives; R^1 and R^3 are the same or different and selected from H, $\text{C}_1 - \text{C}_4$ alkyl chains,
 30 which may include one O, linking R^1 and R^3 to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which

rings optionally bear hydroxyl substituents; R^2 and R^4 are the same or different and selected from H, a nitrate group, C_1 - C_4 alkyl optionally bearing 1-3 nitrate group, and acyl groups ($-C(O)R^5$); and R^7 , R^{11} are the same or different $C_1 - C_8$, alkyl or acyl.

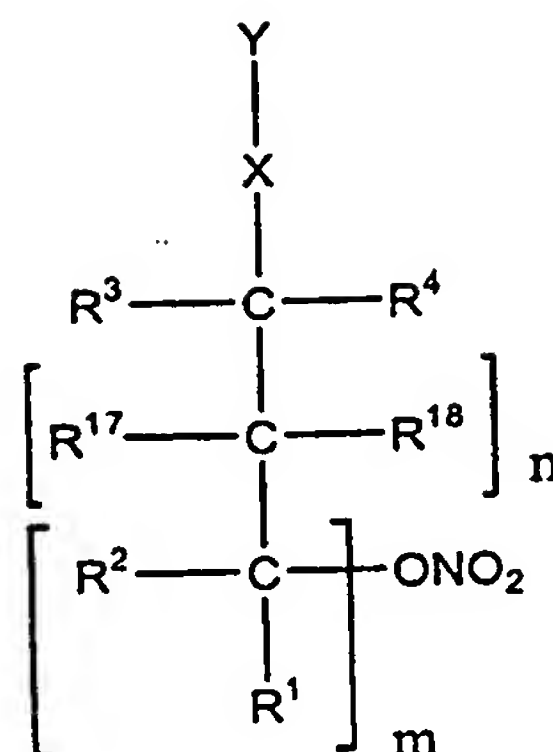
5 In certain embodiments in which R^{19} is X-Y, $m, p = 1$, and $n = 0$.

In other embodiments in which R^{19} is X-Y, X is selected from: CH_2 , O, NH, NMe, CN, NHOH, N_2H_3 , $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3 , S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SH, SR^7 , SO_2M , $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$,
 10 $S(O)_2OR^9$, PO_3HM , PO_3M_2 , $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M , CO_2H , CO_2R^{11} , $C(O)$, $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2M , $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2 , $C(O)(SR^{13})$, and SSR^4 .

In other embodiments in which R^{19} is X-Y, Y is selected from CN, $N_2H_2R^{13}$,
 15 $N_2HR^{13}R^{14}$, N_3 , SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SR^4 , SO_2M , PO_3HM , PO_3M_2 , $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M , CO_2H , CO_2R^{11} , $C(O)R^{12}$, $C(O)(SR^{13})$, SR^5 , SSR^5 , or does not exist.

In certain embodiments, X and/or Y contain a sulfur-containing functional group.
 20 In some embodiments, a compound of the invention according to Formula II comprises a heterocyclic functionality, more preferably, a nucleoside or nucleobase. In further embodiments, a compound of the invention comprises a carbocyclic functionality, more preferably, a steroidal or carbohydrate moiety.

25 In another aspect, a therapeutic compound which is employed in methods of the invention is represented by the formula (Formula III):



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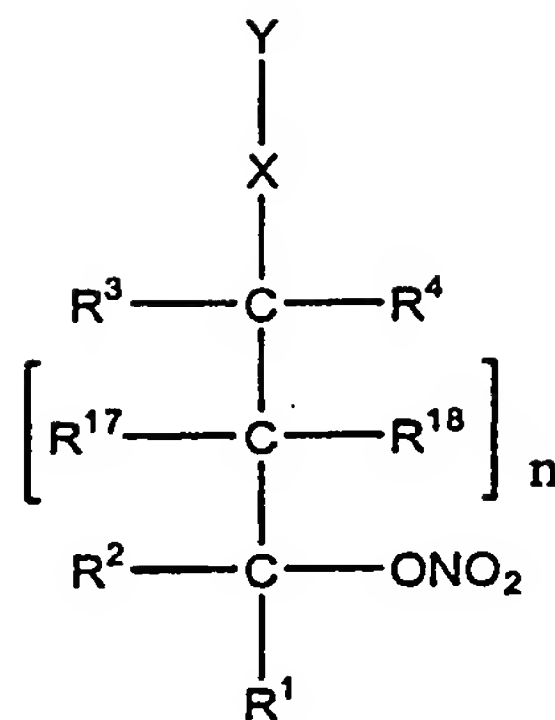
in which: m is 1-10; R^{1-18} , X , and Y have the meaning as defined above. In some embodiments, $R^6 - R^{16}$ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents, or $C_1 - C_6$ connections to $R^1 - R^4$ in cyclic derivatives. In certain preferred embodiments, R^{18} is A and $n = 1$.

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In another aspect, the invention provides novel compounds useful for mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement which are represented by the structures of Formula 3.

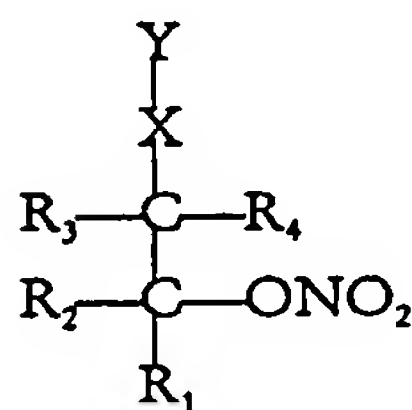
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In a further aspect, a therapeutic compound according to the invention is represented by the formula (Formula IV):



in which: $R^3, R^1 = H$; n, R^2, R^{18}, X , and Y have the meaning as defined above. In certain preferred embodiments, X is CH_2 or does not exist, and Y is selected from: F, Br, Cl, CH_3 , CF_2H , CF_3 , OH, NH_2 , NHR_6 , NR_6R_7 , CN, $NHOH$, N_2H_3 , $N_2H_2R_{13}$, $N_2HR_{13}R_{14}$, N_3 , S, SCN, $SCN_2H_2(R_{15})_2$, $SCN_2H_3(R_{15})$, $SC(O)N(R_{15})_2$, $SC(O)NHR_{15}$, SO_3M , SH, SR_7 , SO_2M , $S(O)R_8$, $S(O)_2R_9$, $S(O)OR_8$, $S(O)_2OR_9$, PO_2HM , PO_3M_2 , $P(O)(OR_{15})(OR_{16})$, $P(O)(OR_{16})(OM)$, $P(O)(R_{15})(OR_8)$, $P(O)(OM)R_{15}$, CO_2M , CO_2H , CO_2R_{11} , $C(O)R_{12}$, $C(O)(OR_{13})$, $C(O)(SR_{13})$, SR_5 , SSR_7 and SSR_5 . In certain embodiments, R_2 and R_4 are optionally H, a nitrate group or a connection to R_5-R_{16} in cyclic derivatives.

By one particular aspect of this invention there is provided an aliphatic nitrate ester containing at least one nitrate group, in which a S or P atom is situated β or γ to a nitrate group, or congeners thereof, having the general formula (Formula IV*):



where X is CH_2 , O, NH, NMe, CN, $NHOH$, N_2H_3 , $N_2H_2R_{13}$, $N_2HR_{13}R_{14}$, N_3 , S, SCN, $SCN_2H_2(R_5)_2$, $SCN_2H_3(R_5)$, $SC(O)N(R_5)_2$, $SC(O)NHR_5$, SO_3M , SH, SR_7 , SO_2M , $S(O)R_8$, $S(O)_2R_9$, $S(O)OR_8$, $S(O)_2OR_9$, PO_3M_2 , $P(O)(OR_5)(OR_6)$, $P(O)(OR_6)(OM)$, $P(O)(R_5)(OR_8)$,

$P(O)(OM)R_5$, CO_2M , CO_2H , CO_2R_{11} , $C(O)$, $C(O)R_{12}$, $C(O)(OR_{13})$, PO_2M , $P(O)(OR_{14})$, $P(O)(R_{13})$, SO , SO_2 , $C(O)(SR_{13})$, SR_4 , or SSR_4 ;

Y is SCN , $SCN_2H_2(R_5)_2$, $SC(O)NHR_5$, $SC(O)N(R_5)_2$, SR_4 , SR_{10} , SSR_{10} , SO_2M , SO_3M , PO_3HM , PO_3M_2 , $P(O)(OR_5)(OR_6)$, or $P(O)(OR_6)(OM)$, CN , N_3 , $N_2H_2R_{13}$,

5 $N_2HR_{13}R_{14}$, CO_2M , CO_2H , CO_2R_{11} , $C(O)R_{12}$, $C(O)(SR_{13})$, or does not exist;

R_5 , R_6 , R_8 , R_9 , R_{10} , R_{12} , R_{13} , R_{14} , R_{15} , R_{16} , are the same or different alkyls containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents or C_1 or C_2 connections to $R_1 - R_3$ in cyclic derivatives;

R_7 , R_{11} are $C_1 - C_8$, alkyl or acyl;

10 R_2 and R_4 are the same or different and selected from H , ONO_2 , $C_1 - C_4$ alkyl optionally bearing 1-3 nitrate groups, and acyl groups ($-C(O)R_{10}$);

R_1 and R_3 are the same or different and selected from H , $C_1 - C_4$ alkyl and chains, which may rings optionally bear hydroxyl substituents; and

15 M is H , Na^+ , K include one O, linking R_1 and R_3 to form pentosyl, hexosyl, cyclopentyl or cyclohexyl rings, which $^+$, NH_4^+ or $N^+H_nR_{11(4-n)}$ where n is 0-3;

with the proviso that, when X is O, Y is not COR_{12} ; and

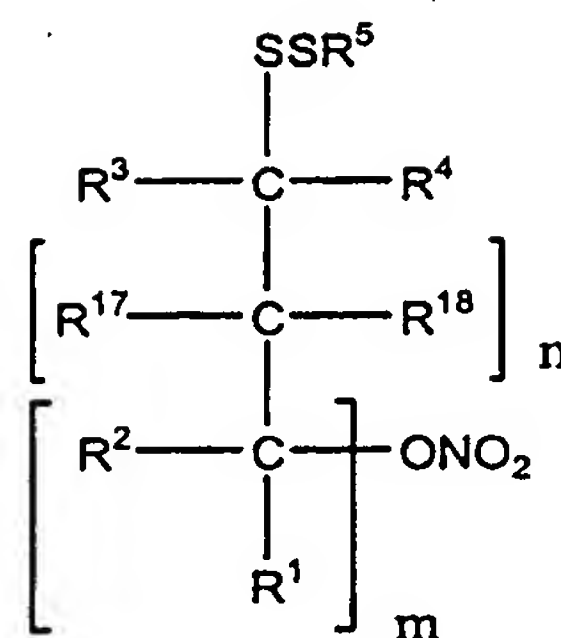
with the proviso that, when R_3 is H, R_6 is not ethyl or n-butyl;

and pharmaceutically acceptable salts thereof.

20 The invention further provides a pharmaceutical composition comprising an effective amount of nitrate ester of Formula IV*, in admixture with a physiologically acceptable carrier therefor. The invention still further provides a method for effecting neuroprotection in a subject in need thereof comprising administering to said subject an effective amount of a nitrate ester of Formula IV*.

25

In yet another aspect of the invention, compounds according to the invention are represented by the formula (Formula V):



where m , n , R^{1-18} , X , and Y have the meaning as defined above.

In another aspect, the invention provides methods for preparing organic nitrates
 5 represented by the structures of Formula V.

The therapeutic compounds of the invention are administered to a subject by a route
 which is effective for mitigating neurodegeneration, effecting neuroprotection and/or
 effecting cognition enhancement. Suitable routes of administration include sublingual,
 10 oral, buccal, transdermal, nasal, subcutaneous, intravenous, intramuscular and
 intraperitoneal injection. Preferred routes of administration are intravenous, subcutaneous
 and transdermal administration, particularly for effecting neuroprotection. In addition,
 for effecting cognition enhancement, oral administration may be preferred. The
 therapeutic compounds can be administered with a pharmaceutically acceptable vehicle.

15

The invention also provides methods for treating a disease state associated with
 neurodegeneration by administering to a subject an effective amount of a therapeutic
 compound having a formula as set forth above, such that a disease state associated with
 neurodegeneration is treated.

20

The invention provides methods for effecting neuroprotection and/or cognition
 enhancement by administering to a subject an effective amount of a therapeutic compound

having a formula described above, such that neuroprotection and/or cognition enhancement is effected.

5 The invention further provides pharmaceutical compositions for treating neurodegeneration. The pharmaceutical compositions include a therapeutic compound of the invention in an amount effective to mitigate neurodegeneration in admixture with a pharmaceutically acceptable carrier therefor.

10 The invention also provides packaged pharmaceutical compositions for treating neurodegeneration. The packaged pharmaceutical compositions include a therapeutic compound of the invention and instructions for using the pharmaceutical composition for treatment of neurodegeneration.

15 BRIEF DESCRIPTION OF DRAWINGS

Figure 1 is a graph showing the effect of GTN with added L-cysteine (2mM) on soluble guanylyl cyclase (GCase) activity in rat aorta homogenate. Bars represent the mean \pm standard errors calculated separately for each point.

20 Figure 2 is a graph showing the effect of IVd neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate normalized to the maximal GTN response. Bars represent the mean \pm standard errors calculated separately for each point.

25 Figure 3 is a graph showing the effect of IVg neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to the maximal GTN response. Bars represent the mean \pm standard errors calculated separately for each point.

Figure 4 is a graph showing the effect of IVb neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean \pm standard errors calculated separately for each point.

5

Figure 5 is a graph showing the effect of IVf neat (diamonds); with added L-cysteine (2mM, triangles; 5mM circles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean \pm standard errors calculated separately for each point.

10

Figure 6 is a graph showing the effect of IVe neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean \pm standard errors calculated separately for each point.

15

Figure 7 is a graph showing the effect of IVj neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean \pm standard errors calculated separately for each point.

20

Figure 8 is a graph showing the effect of IVa neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean \pm standard errors calculated separately for each point.

25

Figure 9 is a graph showing a comparison of GTN (squares), IIIm (circles) and IVh (triangles) with added L-cysteine (1 mM) on soluble GCase activity in rat aorta homogenate (a), and rat hippocampus homogenate (b). Data points represent the mean of duplicate determinations carried out in identical GCase preparations.

Figure 10 is a graph showing a comparison of GTN (squares), Va (circles) and Vb (triangles) with added L-cysteine(1 mM) on soluble GCase activity in rat aorta homogenate homogenate (a), and rat hippocampus homogenate (b). Data points represent the mean \pm standard errors calculated separately for each point (n=8-11).

5

Figure 11 is a graph showing a comparison of cyclic GMP accumulation in isolated rat aorta induced by diluent (Basal, open bar), GTN (filled bar), Va (stippled bar), or IIIIm (hatched bar). Segments of rat aorta were exposed to diluent, 1 μ M drug (a), or 10 μ M drug (b) for 1 min. and cyclic GMP content determined by radioimmunoassay. Data are the mean \pm standard errors (a, n=8; b, n=5).

10

Figure 12 is a graph showing a comparison of cyclic GMP accumulation in isolated rat aorta induced by diluent (Basal, open bar), GTN (filled bar), IVk (stippled bar), Vb (cross-hatched bar), or Vc (hatched bar). Segments of rat aorta were exposed to diluent, 1 μ M drug (a), or 10 μ M drug (b) for 1 min and cyclic GMP content determined by radioimmunoassay. Data are the mean \pm standard errors (a, n=5; b, n=4).

15

Figure 13 is a graph showing cyclic GMP accumulation in rat hippocampal slices induced by diluent (Basal, open bar), GTN (filled bar), and Va (stippled bar). Sections of rat hippocampus (400 μ m) were prepared and exposed to diluent, 10 μ M drug (a) or 100 μ M drug (b) for 3 min and cyclic GMP content determined by radioimmunoassay. Data are the mean \pm standard errors (a, n=4; b, n=5).

20

Figure 14 is a graph showing a comparison of relaxation of isolated rat aorta induced by GTN (squares), Va (open triangles), compound IVc (diamonds), compound IVd (open squares), compound IVf (triangles), and compound IVg (open diamonds). Data points represent the mean \pm standard errors (n=5-8).

25

Figure 15 is a graph showing a comparison of relaxation of isolated rat aorta induced by GTN (squares), IVk (open triangles), Vb (diamonds), IIIIm (open squares), Vc (triangles), and IVh (open diamonds). Data points represent the mean \pm standard errors (n=3-8).

5

Figure 16 is a graph showing relaxation induced by t-Bu nitrosothiol in isolated rat aorta. Data points represent the mean \pm standard deviation (n=3).

Figure 17 is a graph showing relaxation induced by compound Ivd (a) and IVc (b) in untreated (squares) and GTN-tolerant (triangles) isolated rat aorta. Aortae were made tolerant by treatment with 0.5 mM GTN for 30 min. Data points represent the mean \pm standard deviation (n= 3-6).

Figure 18 is a graph showing a comparison of the percent change in mean arterial pressure in conscious unrestrained rats after subcutaneous administration of 400 μ mol/kg GTN (squares) or Va (open circles). Data points represent the mean \pm standard errors (n=6).

Figure 19 is a graph showing a comparison of the percent change in mean arterial pressure in Inactin anaesthetized rats after intravenous bolus injection of GTN (squares) or Va (open circles). Data points represent the mean \pm standard errors (n=4).

Figure 20 is a graph showing plasma levels (μ M) of Vb (circles) and its mononitrate metabolite Vc (open squares) after subcutaneous administration of 200 μ mol/kg Vb in conscious unrestrained rats. Data points represent the mean of two experiments.

Figure 21 is a graph showing the effect of compound Va on lactate dehydrogenase (LDH) release from rat hippocampal slices after a 30-min period of *in vitro* ischemia. Data are the mean \pm standard errors (n=8). *, P< 0.05 compared to ischemia.

Figure 22 is a graph showing the effect of delayed administration of Va on lactate dehydrogenase (LDH) release from rat hippocampal slices after a 30-min period of *in vitro* ischemia. Data are the mean \pm standard errors (n=6). *, P < 0.05 compared to ischemia.

5 Figure 23 is a graph showing the effect of blocking guanylyl cyclase with ODQ on the neuroprotective properties of Va in rat hippocampal slices subjected to a 30-min period of *in vitro* ischemia. Data are the mean \pm standard errors (n=4).

10 Figure 24 is a graph showing viable neurons in the CA1 region of the gerbil hippocampus after global cerebral ischemia. Data are the mean \pm standard error for the number of animals in parentheses. *, P < 0.05 compared to vehicle control.

15 Figure 25 is a graph showing the total and cerebral cortical infarct volume of rat brain after a 2-hour period of focal cerebral ischemia. Data are the mean \pm standard errors (n=10).

Figure 26 is a graph showing the effect of GTN (0.2. or 0.4 mg/hr by subcutaneous patch) on NMDA-induced loss of striatal tyrosine hydroxylase (TH) activity in the rat.

20 Figure 27 is a graph showing the effect of GTN (0.4 mg/hr by subcutaneous patch) implanted one hour after an infusion of NMDA into the substantia nigra on striatal TH activity. ** P < 0.05 compared to animals receiving NMDA alone.

25 Figure 28 is a graph showing the percent decrease in striatal TH activity in rats pretreated with GTN compared to Losartan, a drug that decreases systemic blood pressure through a mechanism different from that of GTN. Animals pretreated with GTN showed significant amounts of neuroprotection; whereas, animals pretreated with Losartan did not show any evidence of neuroprotection.

Figure 29 is a graph showing the blood pressure profiles of animals administered (a) GTN (0.4 mg/hr by subcutaneous patch), or (b) losartan (30 mg/kg by intraperitoneal injection).

5 Figure 30 is a graph showing the effect of compound IVd (Bunte salt, 10-100 μ M) on GABA receptor-activated membrane current recorded in an oocyte expressing the $\alpha 1\beta 2\gamma 2L$ isoform of the GABA_A receptor.

10 Figure 31 is a graph showing that nitric oxide donors have no effect on GABA_A receptors expressed in *Xenopus* oocytes.

Figure 32 is a graph showing that the concentration-response relationship for activation of the GABA_A receptor is altered in a non-competitive manner by compound IVd (Bunte salt).

15

DETAILED DESCRIPTION OF INVENTION

This invention pertains to methods and compositions useful for treating neurodegeneration. The methods of the invention involve administering to a subject a therapeutic compound which effects neuroprotection and/or cognition enhancement. Neuroprotection and/or cognition enhancement can be effected, for example, by modulating an interaction with guanylyl cyclase (GCase), a glutamate or non-glutamate neuroreceptor or attenuating free radical damage. GCase is the enzyme responsible for cGMP production in various areas of the brain.

25 According to certain aspects of the invention, neurodegeneration is mitigated by stimulating cerebral GCase. One of the major targets for organic nitrates is GCase activation, resulting in the production of cGMP. Experimental evidence obtained in a number of *in vitro* model systems supports the notion that elevated levels of cGMP help to prevent apoptotic (programmed) cell death. Thus, a cGMP-dependent mechanism
30 significantly increases the

survival of trophic factor-deprived PC12 cells and rat sympathetic neurons (Farinelli et al., 1996), and of primary cultures of rat embryonic motor neurons (Estevez et al., 1998). The mechanism of action for organic nitrates in preventing apoptotic cell death may be inhibition of caspase-3 activation indirectly through elevations in cGMP levels or directly
5 via protein S-nitrosylation of the enzyme by an NO-intermediate (Kim et al., 1997). Caspase-3 is a member of the cysteine protease family of enzymes that are essential for the execution step in apoptosis (Cohen, 1997; Nicholson and Thornberry, 1997). Activation of caspase-3 is required for apoptotic cell death in trophic factor-deprived PC12 cells (Haviv et al., 1997) and in glutamate-mediated apoptotic cell death of cultured cerebellar granule
10 neurons (Du et al., 1997). In animal models of cerebral ischemia, caspase-3 activity is induced and may be responsible for the apoptotic component of delayed neuronal cell death (Chen et al., 1998; Namura et al., 1998; Ni et al., 1998). Inhibitors of caspase-3 significantly decrease the apoptotic component of delayed neuronal cell death in response to ischemic injury both *in vitro* (Gottron et al., 1997) and *in vivo* (Endres et al., 1998). A
15 secreted region of the Alzheimer's disease β -amyloid precursor protein lowers intracellular calcium levels and provides neuroprotective effects on target cells through increases in cGMP levels and activation of protein kinase G (Barger et al., 1995; Furukawa et al., 1996). In preferred embodiments of the methods of the invention, nitrated molecules that have the capacity to activate GCase directly or via release of an NO-containing intermediate are
20 used to modulate GCase activity.

According to certain other aspects of the invention, cognition enhancement (e.g., improved memory performance) is achieved by stimulating cerebral GCase. Several lines of experimental evidence support the notion that GCase and cGMP are involved in the
25 formation and retention of new information. cGMP has been directly implicated in both long-term potentiation (LTP) and long-term depression (LTD), which are proposed cellular models for learning and memory (Arancio et al., 1995; Wu et al., 1998). In animal models, elevation of hippocampal cGMP levels leading to increased protein kinase G activity has been shown to be important for retention and consolidation of new learning (Bernabeu et
30 al., 1996, 1997). Thus, stimulation of cerebral GCase activity is expected to improve learning and

memory performance in individuals in whom cognitive abilities are impaired by injury, disease, or aging.

We have shown that novel organic nitrate esters have differential effects to activate
5 soluble GCase and to cause cGMP accumulation in vascular and brain tissue. There is a
clear dissociation between the vascular relaxation effects of organic nitrate esters and ability
to effect neuroprotection. Activation of GCase and accumulation of cGMP have been
shown to be important in the neuroprotection of hippocampal brain slices subjected to a
period of *in vitro* ischemia.

10

Cerebral ischemia results in marked increases in the release of the excitatory amino
acid glutamate in the affected brain region (Bullock et al., 1998; Huang et al., 1998; Yang et
al., 1998). In both humans (Bullock et al., 1998) and experimental animals (Huang et al.,
1998; Goda et al., 1998; Yang et al., 1998), the amount of glutamate released during
15 ischemia is positively correlated with the extent of brain injury. In experimental animal
models of cerebral ischemia, decreased release of glutamate during ischemia (Goda et al.,
1998) or blockade of glutamate receptors with antagonists (Ibarrola et al., 1998; O'Neill et
al., 1998; Umemura et al., 1997) significantly reduces the extent of brain injury. However,
these interventions are only effective when given prior to or during the ischemic insult.
20 To be broadly useful, a therapeutic intervention is preferably effective when administered
after the period of ischemia. We have designed a class of novel organic nitrate esters having
high efficacy in effecting neuroprotection *in vivo* in models of transient global and focal
cerebral ischemia when given after the ischemic insult. It will be appreciated, therefore,
that these organic nitrates can be used for treatment of conditions including but not
25 limited to: stroke; Parkinson's disease; Alzheimer's disease; Huntington's disease; multiple
sclerosis; amyotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism;
alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma
to the head; hypoglycemia; hypoxia; myocardial infarction; cerebral vascular occlusion;
cerebral vascular

hemorrhage; hemorrhage; environmental excitotoxins of plant, animal and marine origin; and the like.

The direct effects of organic nitrates on amino acid neurotransmitter receptors has
5 been tested using the *Xenopus* oocyte expression system and two-electrode voltage-clamp
recording methods. Organic nitrates were found to have direct, modulatory effects on
GABA_A receptor function (see Working Examples below). These allosteric modulatory
effects of organic nitrates were not shared by direct NO-generating compounds, indicating
a novel mechanism of action for organic nitrates to interact with GABA_A receptors. In
10 behavioural models of learning and memory, drugs which decrease GABA_A receptor
function improve performance on learning and memory tasks (Venault et al., 1992). Thus,
the behavioural effect of organic nitrates, developed to act as modulators of GABA_A
receptor function, will be to improve memory performance and cognition in patient
populations. It will be appreciated, therefore, that these organic nitrates can be used for
15 treatment of conditions including but not limited to: stroke; dementias of all type; trauma;
drug-induced brain damage; and aging.

According to certain aspects of the invention, neurodegeneration is mitigated by
inhibition of free radical damage. Reoxygenation and reperfusion after a period of
20 ischemia contributes significantly to the development of brain injury. Oxygen radicals,
especially superoxide and peroxynitrite, formed in the period after an ischemic event may
initiate processes such as breakdown of membrane lipids (lipid peroxidation), leading to
loss of cell membrane integrity and inhibition of mitochondrial function (Macdonald and
Stoodley, 1998; Gaetani et al, 1998). Oxidative stress is also believed to be one factor
25 involved in initiation of apoptotic neuronal cell death (Tagami et al., 1998). In
experimental animal models of ischemic brain injury, free radical scavengers and enhanced
activity of superoxide dismutase have been found to reduce the extent of neuronal injury
and cell death (Chan et al., 1998; Mizuno et al., 1998; Tagami et al., 1998). In preferred
embodiments of the methods of the invention, nitrated molecules which have the capacity
30 to inhibit production of free radicals and/or which act as free radical scavengers are used to
attenuate the brain injury that occurs

after a period of cerebral ischemia. It will be appreciated by those skilled in the art, that any organic nitrate in which vasodilatory potency is reduced and neuroprotective potency increased, represents a new and useful therapeutic agent for use in neuroprotection, particularly in treatment of conditions including but not limited to: stroke; Parkinson's
5 disease; Alzheimer's disease; Huntington's disease; multiple sclerosis; amyotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism; alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma to the head; hypoglycemia; hypoxia; myocardial infarction; cerebral vascular occlusion; cerebral vascular hemorrhage; hemorrhage; environmental excitotoxins of plant, animal and marine origin. GTN itself,
10 proposed as a neuroprotective agent, has no clinical utility as a neuroprotective agent in therapy owing to its extraordinarily high vasodilatory potency. Similarly, by extrapolation, 1,2,3-trinitratopropane (GTN) derivatives are not expected to have clinical utility as neuroprotective agents in therapy owing to their especially high vasodilatory potency.

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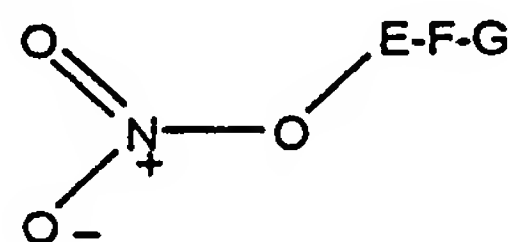
It will additionally be appreciated by those skilled in the art, that the use in therapy of any organic nitrate in cognition enhancement, represents a new and useful treatment for cognition enhancement, particularly in treatment of conditions including but not limited to: stroke; dementias of all type, trauma, drug-induced brain damage, and aging.

20

"Mitigating neurodegeneration" as use herein involves effecting neuroprotection, inhibiting or preventing neurodegeneration, and/or ameliorating the manifestations or impact of neurodegeneration. Such amelioration includes effecting cognition enhancement, as is quantified by tests known in the art (e.g., Venault et al., 1992,
25 incorporated herein by reference). "Modulating" a biological process as used herein (for example, modulating the activity of the non-glutamate neuroreceptors), encompasses both increasing (positively modulating) and decreasing (negatively modulating) such activity, and thus inhibition, potentiation, agonism, and antagonism of the biological process.

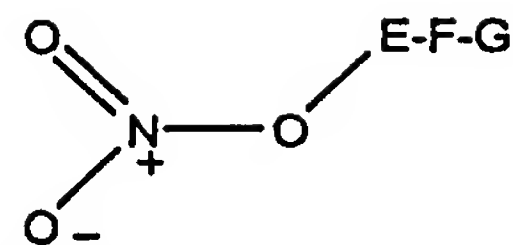
In particular, the therapeutic compounds of the invention comprise at least one nitrate group. The nitrate groups(s) can optionally be covalently bound to a carrier moiety or molecule (e.g., an aromatic group, an aliphatic group, peptide, steroid, nucleoside, peptidomimetic, steroidomimetic, or nucleoside analogue, or the like). In addition to
5 functioning as a carrier for the nitrate functionality, the carrier moiety or molecule can enable the compound to traverse biological membranes and to be biodistributed preferentially, without excessive or premature metabolism. Further, in addition to functioning as a carrier for the nitrate functionality, the carrier moiety or molecule can enable the compound to exert amplified neuroprotective effects and/or cognition
10 enhancement through synergism with the nitrate functionality.

In one aspect, the invention provides a method of treating a neurological condition and/or preventing an undesirable mental condition (e.g., memory loss) including the step of administering to a subject an effective amount of a therapeutic compound capable of
15 mitigating neurodegeneration which has at least one nitrate group. In one embodiment, the therapeutic compound is capable of effecting neuroprotection. In another embodiment of the invention, the therapeutic compound is capable of effecting cognition enhancement. The therapeutic compound has the formula (Formula I):



20 wherein E, F, G are organic radicals which may contain inorganic counterions; so that a neurological condition is treated.

In another aspect, the invention provides a pharmaceutical composition including a physiologically acceptable carrier and a compound having the formula (Formula I):



wherein: E, F, G are organic radicals which may contain inorganic counterions; such that neurodegeneration is mitigated. The composition is employed for mitigating neurodegeneration, effecting neuroprotection and /or effecting cognition enhancement.

5 In another aspect, therapeutic compounds of the invention that effect neuroprotection and/or effect cognition enhancement in a subject to which the therapeutic compound is administered have the formula (Formula II):



10 in which: m, n, p are integers from 0 to 10; $\text{R}^{3,17}$ are each independently hydrogen, a nitrate group, or A; $\text{R}^{4,4}$ are each independently hydrogen or A, where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains
15 O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains
20 O, S, NR^6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety
25 constituting a linkage of from 0 to 5

carbons, between R^1 and R^3 and/or between R^{17} and R^4 , which optionally contains O, S, NR^6 and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g., $C=O$, $C=S$, $C=NOH$), which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylaryl amino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy; R^2 , R^5 , R^{18} , R^{19} are optionally hydrogen, A, or X-Y; where X is F, Br, Cl, NO_2 , CH_2 , CF_2 , O, NH, NMe, CN, $NHOH$, N_2H_3 , $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3 , S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SH, SR^7 , SO_2M , $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM , PO_3HM , PO_3M_2 , $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M , CO_2H , CO_2R^{11} , $C(O)$, $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2H , PO_2M , $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2 , $C(O)(SR^{13})$, SR^5 , SSR^7 or SSR^5 ; Y is F, Br, Cl, CH_3 , CF_2H , CF_3 , OH, NH_2 , NHR^6 , NR^6R^7 , CN, $NHOH$, N_2H_3 , $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3 , S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SH, SR^7 , SO_2M , $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM , PO_3M_2 , $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M , CO_2H , CO_2R^{11} , $C(O)R^{12}$, $C(O)(OR^{13})$, $C(O)(SR^{13})$, SR^5 , SSR^7 or SSR^5 , or does not exist; R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents; or $C_1 - C_6$ connections to $R^1 - R^4$ in cyclic derivatives; or are each independently hydrogen, a nitrate group, or A; M is H, Na^+ , K^+ , NH_4^+ , $N^+H_kR^{11}_{(4-k)}$ where k is 0-3, or other pharmaceutically acceptable counterion.

Pharmaceutical compositions comprising a compound of Formula II in admixture with a pharmaceutically acceptable carrier therefor are provided by the invention. The invention further provides methods of mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement in a subject comprising the step of administering a

compound of Formula II to a subject such that said mitigation and /or said neuroprotection an/or cognition enhancement occurs.

According to this aspect of the invention, preferred therapeutic compounds for effecting neuroprotection and/or cognition enhancement in a subject to which the compound is administered include compounds in which R^{19} is X-Y. In some preferred embodiments: R^{19} is X-Y and $R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$ are the same or different alkyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents, or C_1 or C_2 connections to $R^1 - R^3$ in cyclic derivatives; R^1 and R^3 are the same or different and selected from H, C_1-C_4 alkyl chains, which may include one O, linking R^1 and R^3 to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which rings optionally bear hydroxyl substituents; R^2 and R^4 are the same or different and selected from H, a nitrate group, C_1-C_4 alkyl optionally bearing 1-3 nitrate group, and acyl groups ($-C(O)R^5$); and R^7, R^{11} are the same or different $C_1 - C_8$, alkyl or acyl.

15

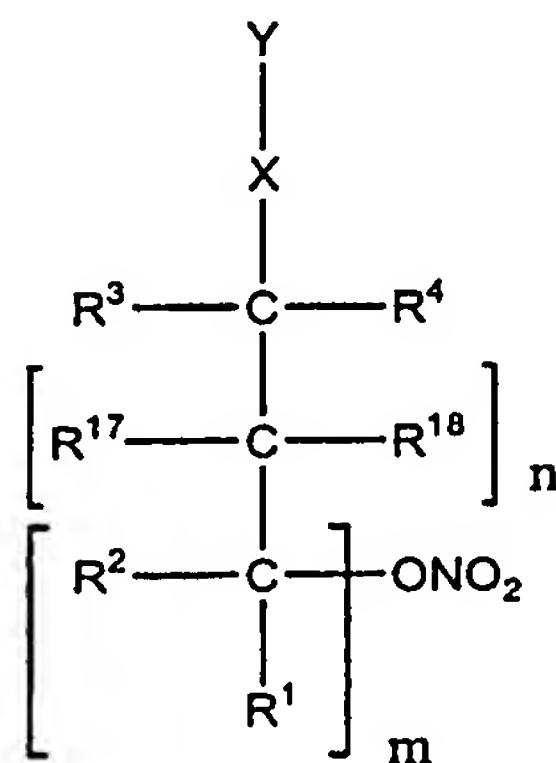
In certain embodiments in which R^{19} is X-Y, $m, p = 1$, and $n = 0$. In other embodiments in which R^{19} is X-Y, X is selected from: $CH_2, O, NH, NMe, CN, NHOH, N_2H_3, N_2H_2R^{13}, N_2HR^{13}R^{14}, N_3, S, SCN, SCN_2H_2(R^{15})_2, SCN_2H_3(R^{15}), SC(O)N(R^{15})_2, SC(O)NHR^{15}, SO_3M, SH, SR^7, SO_2M, S(O)R^8, S(O)_2R^9, S(O)OR^8, S(O)_2OR^9, PO_3HM, PO_3M_2, P(O)(OR^{15})(OR^{16}), P(O)(OR^{16})(OM), P(O)(R^{15})(OR^8), P(O)(OM)R^{15}, CO_2M, CO_2H, CO_2R^{11}, C(O), C(O)R^{12}, C(O)(OR^{13}), PO_2M, P(O)(OR^{14}), P(O)(R^{13}), SO, SO_2, C(O)(SR^{13}), SSR^4$. In certain other embodiments in which R^{19} is X-Y, Y is selected from $CN, N_2H_2R^{13}, N_2HR^{13}R^{14}, N_3, SCN, SCN_2H_2(R^{15})_2, SC(O)N(R^{15})_2, SC(O)NHR^{15}, SO_3M, SR^4, SO_2M, PO_3HM, PO_3M_2, P(O)(OR^{15})(OR^{16}), P(O)(OR^{16})(OM), P(O)(R^{15})(OR^8), P(O)(OM)R^{15}, CO_2M, CO_2H, CO_2R^{11}, C(O)R^{12}, C(O)(SR^{13}), SR^5, SSR^5$, or does not exist.

25

In some embodiments, X and/or Y contains a sulfur-containing functional group. In certain embodiments, the compound of the invention comprises a heterocyclic functionality, more preferably, a nucleoside or nucleobase. In other embodiments, the compound of the invention comprises a carbocyclic functionality, more preferably, a steroidal or carbohydrate moiety.

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In another aspect of the invention, a therapeutic compound of the invention is represented by the formula (Formula III):



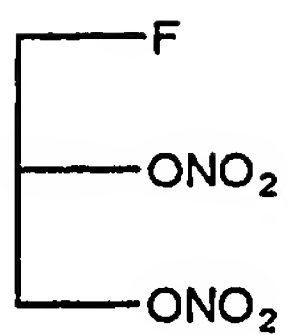
5 in which: m, n are 1-10; R^{1-18} , X, and Y have the meaning as defined above. In certain preferred embodiments, $R^6 - R^{16}$ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents, or $C_1 - C_6$ connections to $R^1 - R^4$ in cyclic derivatives. In certain preferred embodiments, R^{18} is A and $m = n = 1$.

10

Pharmaceutical compositions comprising a compound of Formula III in admixture with a pharmaceutically acceptable carrier therefor are provided by the invention. The invention further provides methods of mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement in a subject comprising the step
 15 of administering a compound of Formula III to a subject such that said mitigation and /or said neuroprotection and/or cognition enhancement occurs.

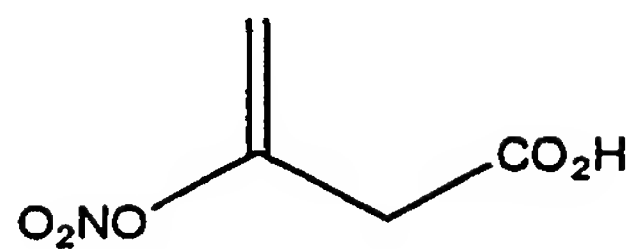
Examples and preferred embodiments of compounds of the invention according to Formula III are set forth below:

IIIa



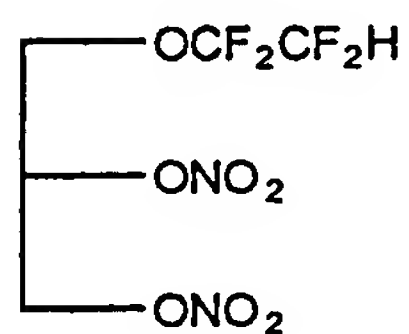
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IIIb



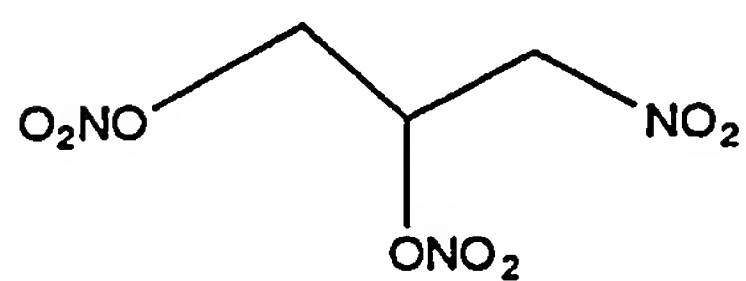
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IIIc



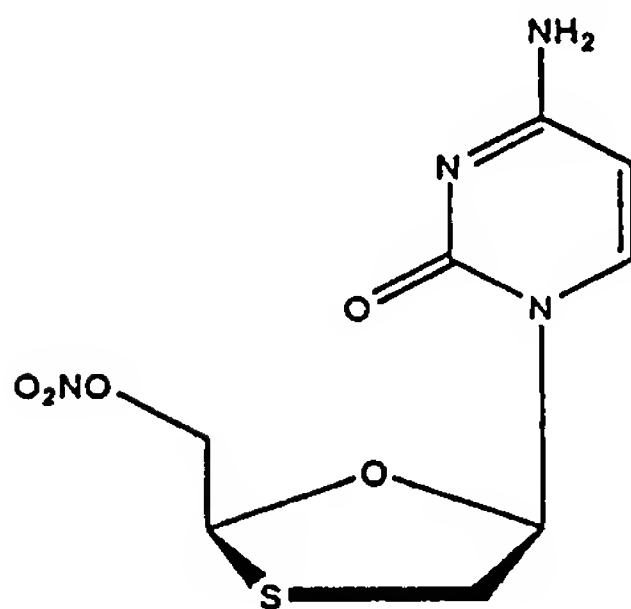
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IIId



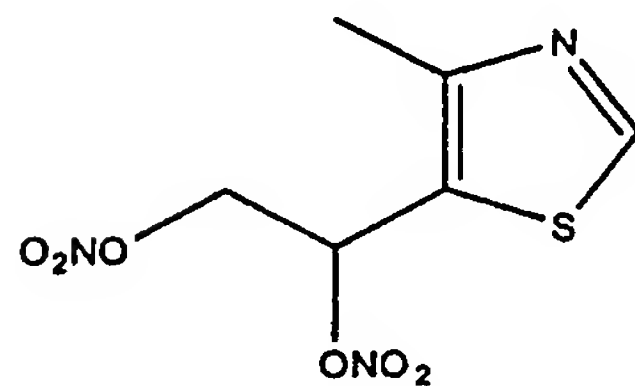
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IIIe

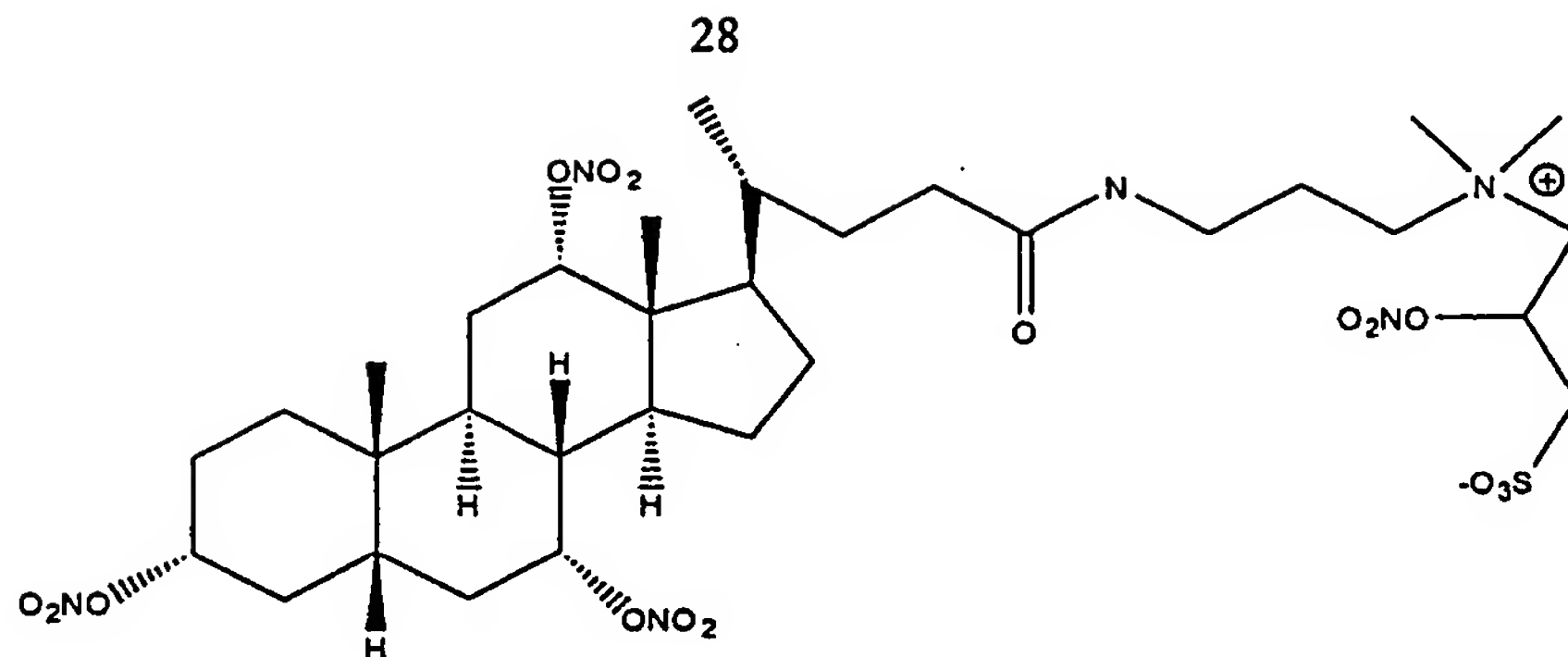


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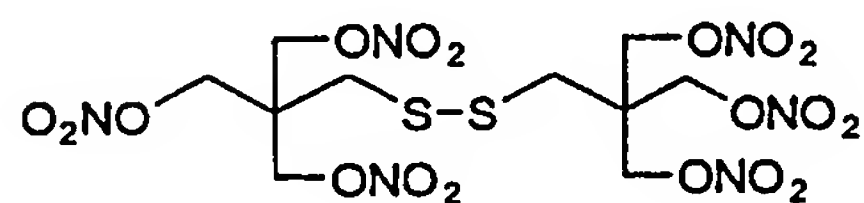
III f



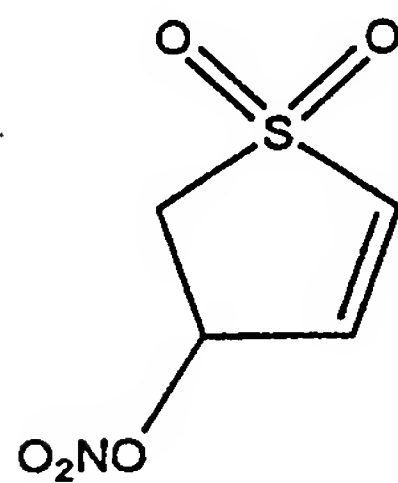
IIIg



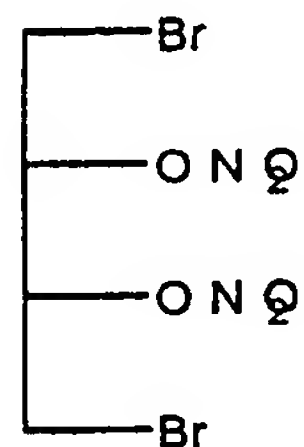
IIIh



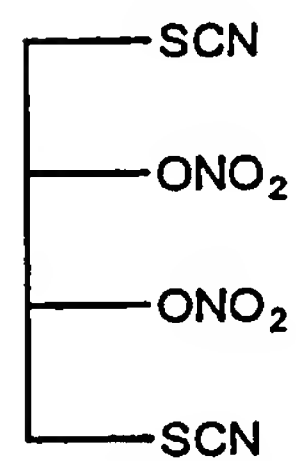
IIIi



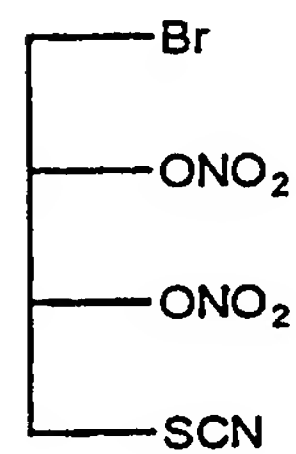
IIIj



IIIk

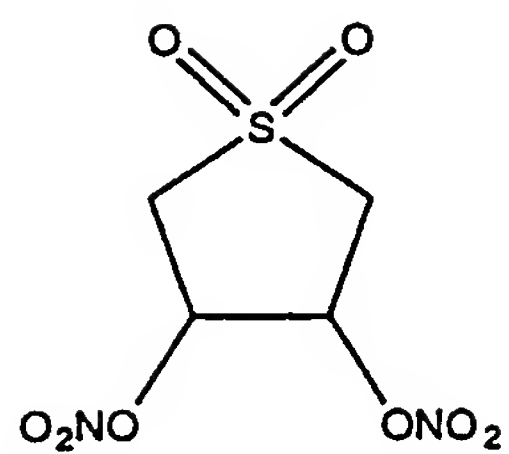


III

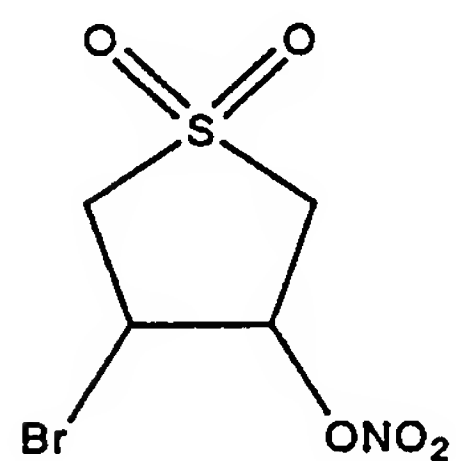


III_m

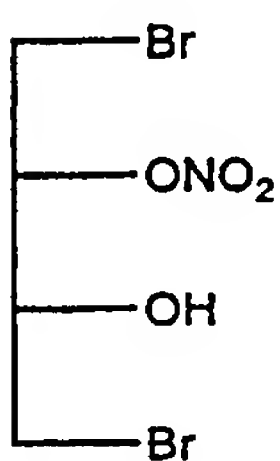
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III_n

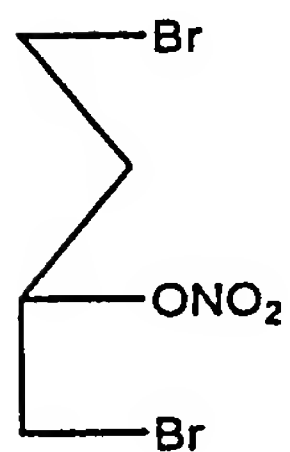
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III_o

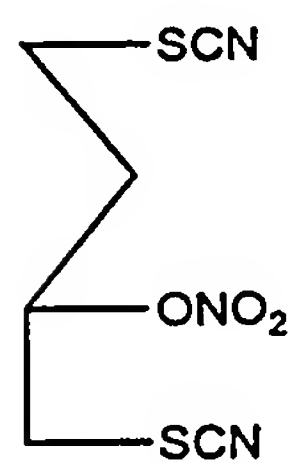
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III_p

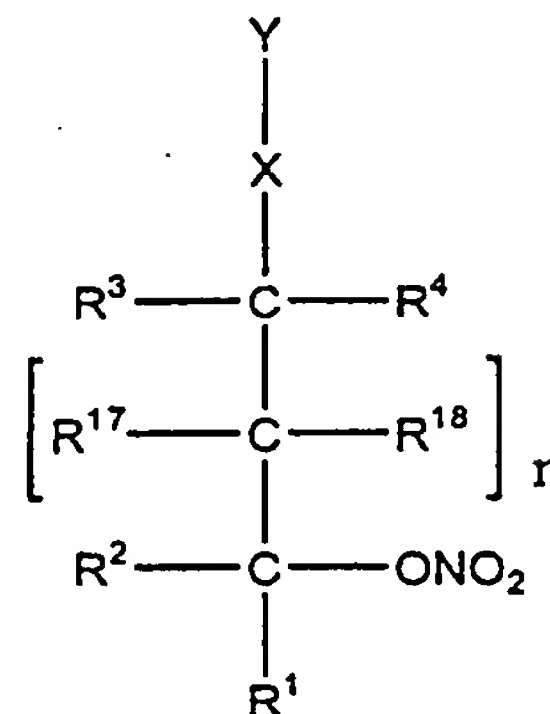
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III_q

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III_q

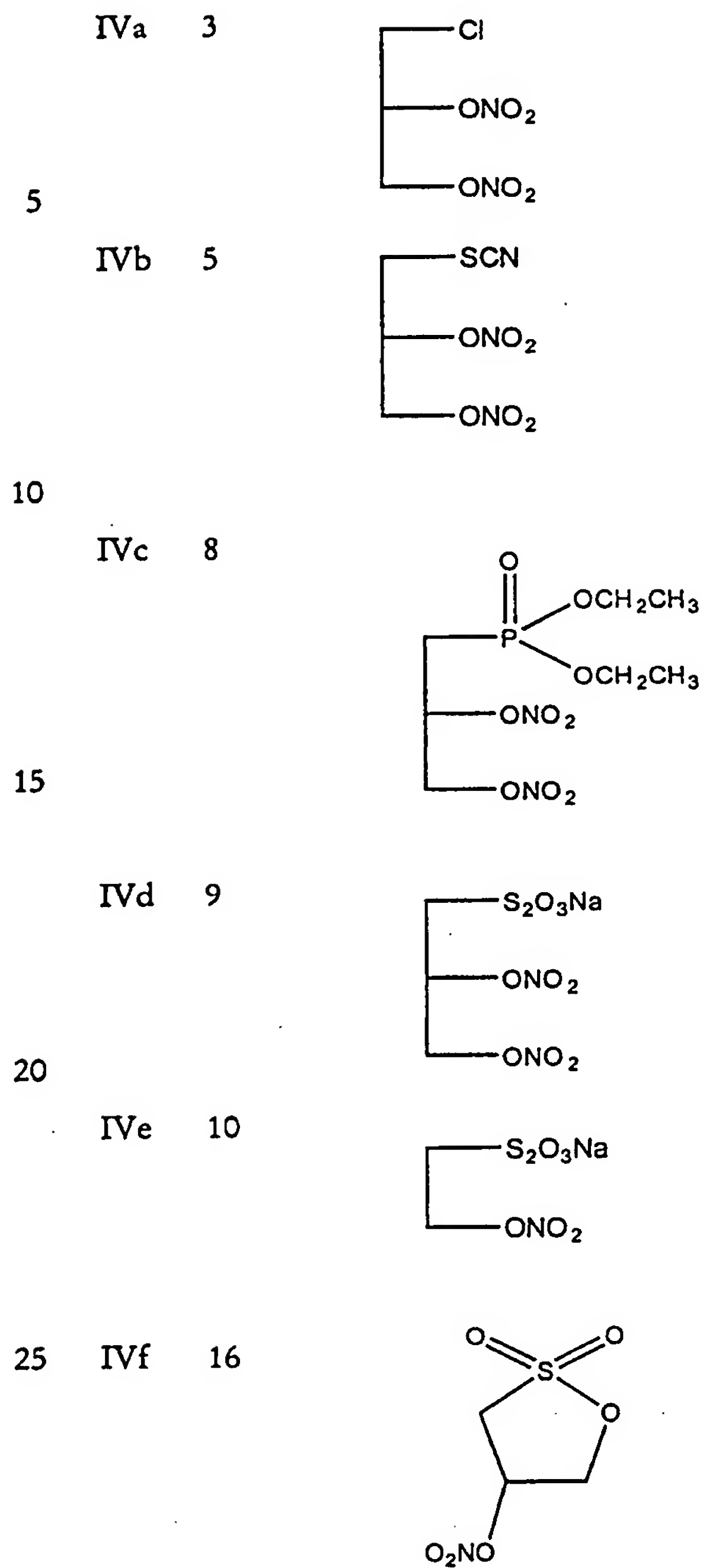
In another aspect of the invention, a therapeutic compound of the invention can be represented by the formula (Formula IV):



in which $n = 0$, X is CH_2 or does not exist, and Y is selected from F , Br , Cl , CH_3 , CF_2H , CF_3 , OH , NH_2 , NHR_6 , NR_6R_7 , CN , $NHOH$, N_2H_3 , $N_2H_2R_{13}$, $N_2HR_{13}R_{14}$, N_3 , S , SCN , $SCN_2H_2(R_{15})_2$, $SCN_2H_3(R_{15})$, $SC(O)N(R_{15})_2$, $SC(O)NHR_{15}$, SO_3M , SH , SR_7 , SO_2M , $S(O)R_8$, $S(O)_2R_9$, $S(O)OR_8$, $S(O)_2OR_9$, PO_2HM , PO_3M_2 , $P(O)(OR_{15})(OR_{16})$, $P(O)(OR_{16})(OM)$, $P(O)(R_{15})(OR_8)$, $P(O)(OM)R_{15}$, CO_2M , CO_2H , CO_2R_{11} , $C(O)R_{12}$, $C(O)(OR_{13})$, $C(O)(SR_{13})$, SR_5 , SSR_7 or SSR_5 . R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} , and R_{16} are as defined above. In certain preferred embodiments, R_2 and R_4 are optionally H , a nitrate group or a connection to R_5 - R_{16} in cyclic derivatives.

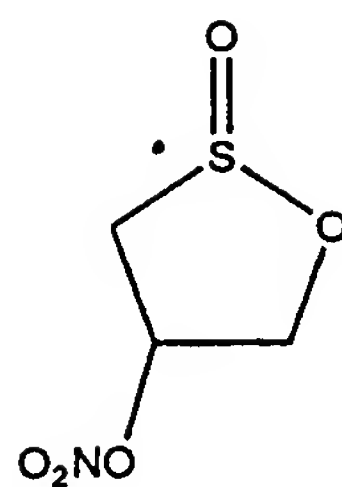
Pharmaceutical compositions comprising a compound of Formula IV in admixture with a pharmaceutically acceptable carrier therefor are provided by the invention. The invention further provides methods of mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement in a subject comprising the step of administering a compound of Formula IV to a subject such that said mitigation and/or said neuroprotection and/or cognition enhancement occurs.

Examples and preferred embodiments of compounds of the invention according to Formula IV are set forth below:



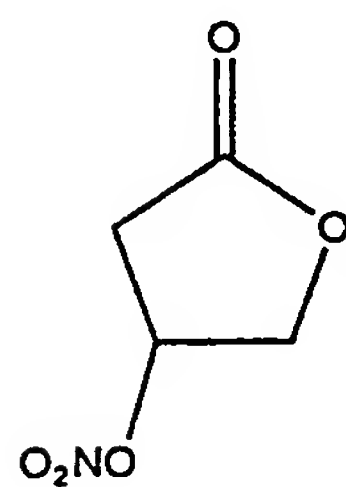
IVg 17

5



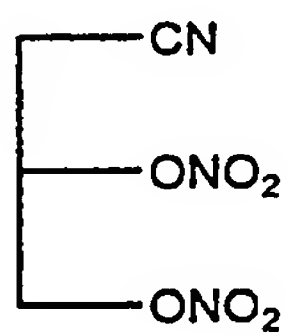
IVh 18

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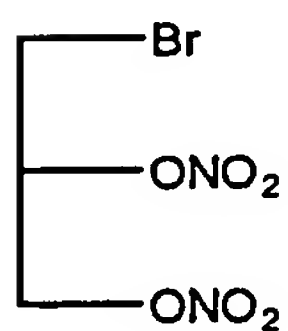
IVi

15



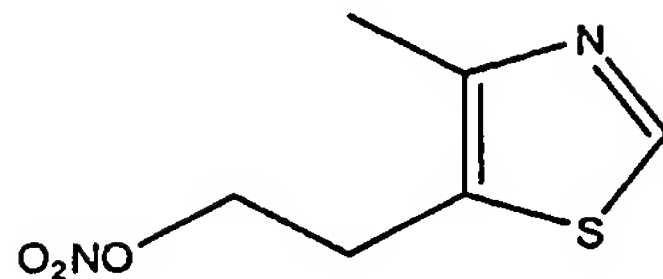
IVj

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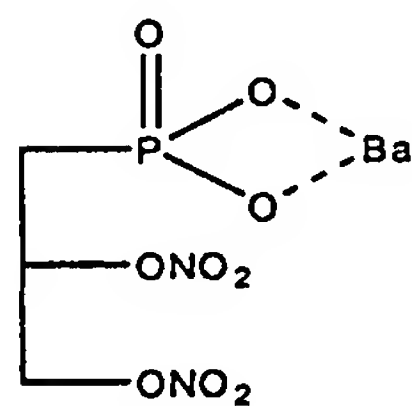


IVk 61

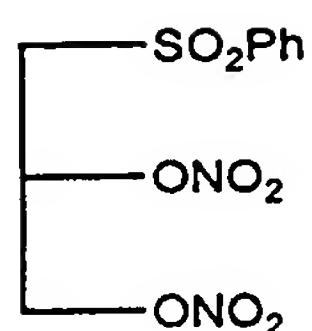
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IVl

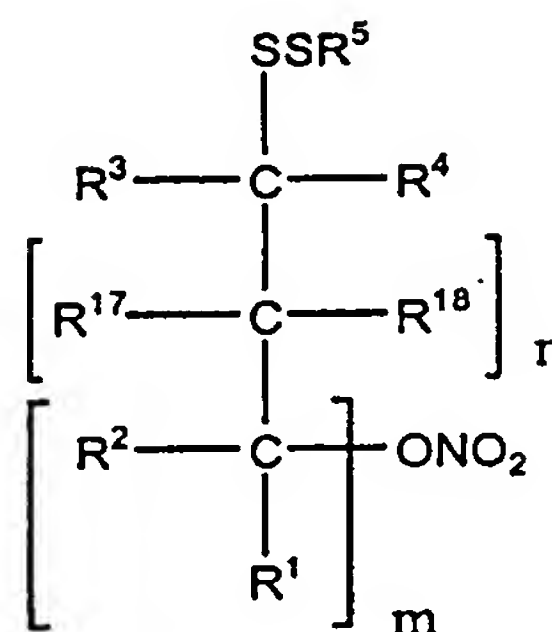


IVm



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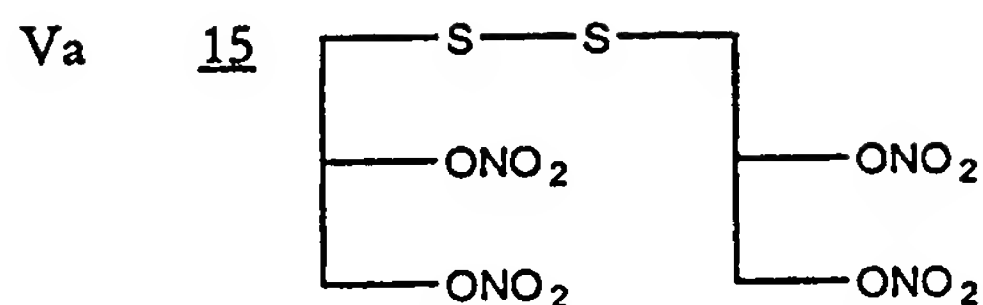
In yet another aspect of the invention, a compound of the invention can be represented by the formula (Formula V):



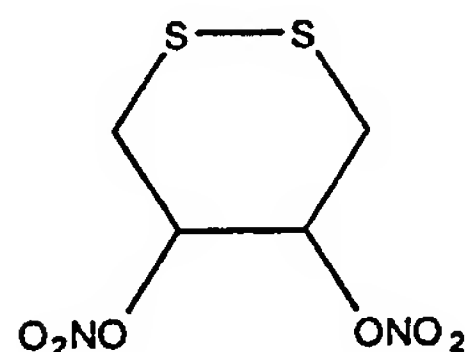
10 in which R_2 is optionally H or a connection to R_5 in cyclic derivatives, R_4 is H or a nitrate group, and R_5 is as described above.

Pharmaceutical compositions comprising a compound of Formula V in admixture with a pharmaceutically acceptable carrier therefor are provided by the invention. The invention further provides methods of mitigating neurodegeneration, effecting
 15 neuroprotection and/or effecting cognition enhancement in a subject comprising the step of administering a compound of Formula V to a subject such that said mitigation and /or said neuroprotection and/or cognition enhancement occurs.

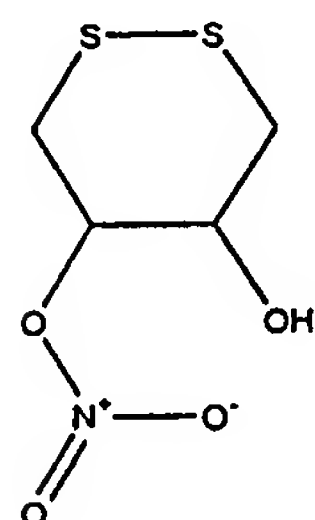
20 Examples and preferred embodiments of compounds of the invention according to formula V (Formulae Va-c) are set forth below:



5 Vb 33



10 Vc 50



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Table 1 lists data determined for compounds of the invention per art-recognized characterization techniques.

Table 1	¹ H NMR	¹³ C NMR
IIIa	(CDCl ₃): 5.34-5.57 (1H, dm, ³ J _{HF} 20.6), 4.53-4.87 (4H, superposition several multiplets, O ₂ NO-CH ₂ + CH ₂ F, ² J _{HF} 46.7, ⁴ J _{HF} 0.66)	(CDCl ₃): 79.47 (d, ¹ J _{CF} 177), 76.73 (d, ² J _{CF} 20.6), 67.84 (d, ³ J _{CF} 6.87)
IIIb	(CDCl ₃): δ	(CDCl ₃): δ
IIIc	(CDCl ₃): δ 5.7 (1H, t, ² J _{HF} 54), 5.45 (1H, m), 4.5-4.9 (2H, m), 4.15-4.35 (1H, m)	(CDCl ₃): δ 75.55, 68.05, 60.76
IIId	(CDCl ₃): δ 5.46 (1H, m), 4.80-4.87 (1H, dd, J 3.5, 12.9), 4.65-4.72 (1H, dd, J 6.2, 12.9), 3.7-3.8 (2H, m)	(CDCl ₃): δ 77.24, 68.57, 39.86
IIIe	(CDCl ₃) δ 8.72 (s, 1H), 5.38 (t, 1H), 4.6 (d, 2H), 2.45 (s, 3H)	-
IIIg	(DMSO-d ₆) CHONO ₂ only: δ 4.8-5.8	(DMSO-d ₆) CONO ₂ only: δ 85.68, 84.17, 82.47, 76.50

IIIh	(CD ₃ OD) δ 4.85 (3H, m), 3.5 (1H, m)	(CD ₃ OD) δ 70.61, 36.74
IIIi	(CDCl ₃): δ 6.95 (dd, 1H), 6.71 (dd, 1H), 6.09 (m, 1H), 3.80 (dd, 1H), 3.32 (dd, 1H)	(CDCl ₃): δ 137.9, 132.5, 76.6, 52.9
IIIj	(CDCl ₃): δ 5.62 (2H, m), 3.60 (4H, m)	(CDCl ₃): δ 77.87, 25.22
IIIk	(CD ₃ CN): δ 3.45 (m, 2H), 5.72 (m, 2H)	(CD ₃ CN): δ 79.98, 28.87
IIIl	-	(CD ₃ CN): δ 79.48, 33.45, 28.47
IIIm	(DMSO-d ₆): δ 5.97 (m, 2H), 3.80 (m, 4H)	(DMSO-d ₆): δ 78.84, 52.60
III n	(CDCl ₃): δ 5.73 (m, 1H), 4.62 (m, 1H), 3.96-3.77 (m, 1H), 3.58-3.32 (m, 1H)	(CDCl ₃): δ 81.47, 57.85, 53.50, 38.75
IIIo	-	(CDCl ₃): δ 81.24, 69.79, 33.26, 27.24
IIIp	(CDCl ₃): δ 5.36 (m, 1H), 3.11-3.60 (m, 4H), 2.33 (m, 2H)	(CDCl ₃): δ 78.92, 33.66, 30.64, 27.36
IIIq	(CDCl ₃): δ 5.47 (m, 1H), 3.53-3.05 (m, 4H), 2.29 (m, 2H)	(CDCl ₃): δ 81.32, 37.12, 32.97, 30.98
IVi	(CDCl ₃): δ 5.45 (1H, m), 4.83 (1H, dd), 4.65 (1H, dd), 2.9 (2H, m)	(CD ₃ OD): δ 116.44, 75.37, 71.20, 19.19
IVk	(CDCl ₃): δ 8.55 (s, 1H), 4.55 (t, 2H), 3.15 (t, 2H), 2.37 (s, 3H)	(CDCl ₃): δ 150.9, 150.7, 125.3, 72.53, 24.47, 15.18
IVm	(CDCl ₃): δ 7.5-8.0 (arom, 5H), 5.7 (1H, m), 4.94 (1H, dd), 4.62 (1H, dd), 3.5 (2H, m)	(CDCl ₃): δ 135.45, 134.79, 129.81, 27.95, 73.08, 70.04, 54.73
Vb	(CDCl ₃): δ 5.56 (m, 2H), 3.38-2.95 (m, 4H)	(CD ₃ OD): δ 85.93, 32.77
Vc	(CDCl ₃): δ 5.85-5.91 (1H, m), 4.50-4.58 (1H, m), 3.22-3.29 (1H, dd, J 5.47, 12.78), 2.97-3.05 (1H, dd, J 4.6, 11.88), 2.82-2.90 (1H, dd, J 2.87, 12.78), 2.74-2.83 (1H, dd, J 3.15, 11.9)	(CDCl ₃): δ 87.6, 74.96, 36.20, 31.54

Methods for preparing organic nitrates represented by the structures of Formula III are provided by the invention and taught herein, particularly in the Working Examples below.

5

It will be noted that the structure of some of the compounds of this invention includes asymmetric carbon atoms. It is to be understood accordingly that the isomers (e.g., enantiomers, diastereomers) arising from such asymmetry are included within the scope of this invention. Such isomers can be obtained in substantially pure form by classical separation techniques and by asymmetric synthesis. For the purposes of this application, unless

10

expressly noted to the contrary, a compound shall be construed to include both the R and S stereoisomers at each stereogenic center.

In certain embodiments, a therapeutic compound of the invention comprises a cation (i.e., in certain embodiments, one of X or Y includes a cation, e.g., in the compound of formula IVd). If the cationic group is a proton, then the compound is considered an acid. If the proton is replaced by a metal ion or its equivalent, the compound is a salt. Pharmaceutically acceptable salts of the therapeutic compound are within the scope of the invention. For example, M can be a pharmaceutically acceptable alkali metal (e.g. Li, Na, K), ammonium, alkaline earth metal (e.g. Ca, Ba, Mg), higher valency cation, or polycationic counter ion (e.g., polyammonium cation) (see e.g., Berge et al., 1977). It will be appreciated that the stoichiometry of an anionic portion of the compound to a salt-forming cation will vary depending on the charge of the anionic portion of the compound and the charge of the counterion. Preferred pharmaceutically acceptable salts include a sodium, potassium, or calcium salt, but other salts are also contemplated within their pharmaceutically acceptable range.

The therapeutic compound of the invention can be administered in a pharmaceutically acceptable vehicle. As used herein "pharmaceutically acceptable vehicle" includes any and all solvents, excipients, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like which are compatible with the activity of the compound and are physiologically acceptable to the subject. An example of the pharmaceutically acceptable vehicle is buffered normal saline (0.15 M NaCl). The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the therapeutic compound, use thereof in the compositions suitable for pharmaceutical administration is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Carrier or substituent moieties useful in the present invention may also include moieties which allow the therapeutic compound to be selectively delivered to a target organ. For example, delivery of the therapeutic compound to the brain may be enhanced by a carrier moiety using either active or passive transport (a "targeting moiety").

5 Illustratively, the carrier molecule may be a redox moiety, as described in, for example, U.S. Patents 4,540,654 and 5,389,623, both to Bodor. These patents disclose drugs linked to dihydropyridine moieties which can enter the brain, where they are oxidized to a charged pyridinium species which is trapped in the brain. Thus drugs accumulate in the brain. Other carrier moieties include compounds, such as amino acids or thyroxine, which
10 can be passively or actively transported *in vivo*. Such a carrier moiety can be metabolically removed *in vivo*, or can remain intact as part of an active compound. Structural mimics of amino acids (and other actively transported moieties) including peptidomimetics, are also useful in the invention. As used herein, the term "peptidomimetic" is intended to include peptide analogues which serve as appropriate substitutes for peptides in interactions with,
15 for example, receptors and enzymes. The peptidomimetic must possess not only affinity, but also efficacy and substrate function. That is, a peptidomimetic exhibits functions of a peptide, without restriction of structure to amino acid constituents. Peptidomimetics, methods for their preparation and use are described in Morgan et al. (1989), the contents of which are incorporated herein by reference. Many targeting moieties are known, and
20 include, for example, asialoglycoproteins (see e.g., Wu, U.S. Patent 5,166,320) and other ligands which are transported into cells via receptor-mediated endocytosis (see below for further examples of targeting moieties which may be covalently or non-covalently bound to a target molecule).

25 In the methods of the invention, neurodegeneration in a subject is mitigated, and/or neuroprotection and/or cognition enhancement is effected, by administering a therapeutic compound of the invention to the subject. The term "subject" is intended to include living organisms in which the particular neurological condition to be treated can occur. Examples of subjects include humans, apes, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and
30 transgenic species thereof. As would be apparent to a person of skill in the art, the animal

subjects employed in the working examples set forth below are reasonable models for human subjects with respect to the tissues and biochemical pathways in question, and consequently the methods, therapeutic compounds and pharmaceutical compositions directed to same. As evidenced by Mordenti (1986) and similar articles, dosage forms for
5 animals such as, for example, rats can be and are widely used directly to establish dosage levels in therapeutic applications in higher mammals, including humans.

In particular, the biochemical cascade initiated by cerebral ischemia is generally accepted to be identical in mammalian species (Mattson and Scheff, 1994; Higashi et al.,
10 1995). In light of this, pharmacological agents that are neuroprotective in animal models such as those described herein are believed to be predictive of clinical efficacy in humans, after appropriate adjustment of dosage. Specifically, there are comparable memory-deficit patterns between brain-damaged rats and humans, which indicates that the rat can serve as an excellent animal model to evaluate the efficacy of pharmacological treatments or brain
15 damage upon memory (Kesner, 1990). The only approved drug for the clinical treatment of occlusive stroke in humans is tissue plasminogen activator, which is administered at a dose of 0.9 mg/kg by intravenous injection (Wittkowsky, 1998). This drug is also effective in protecting the rat brain subjected to cerebral ischemia by occlusion of the middle cerebral artery, when administered at a dose of 10 mg/kg intravenously (Jiang et al., 1998).
20 Thus, the rat model of focal cerebral ischemia used in the development of the novel organic nitrate esters described herein has been shown to be shown to be predictive of clinical efficacy with at least one other class of pharmacological agents.

As would also be apparent to a person skilled in the art, the invention further
25 encompasses methods of the invention employed *ex vivo* or *in vitro*. For example, the Working Examples describe studies utilizing tissue homogenates according to the invention. Furthermore, diagnostic tests or studies of efficacy of selected compounds may conveniently be performed *ex vivo* or *in vitro*, including in animal models. Such tests, studies and assays are within the scope of the invention.

Administration of the compositions of the present invention to a subject to be treated can be carried out using known procedures, at dosages and for periods of time effective to mitigate neurodegeneration, and/or to effect neuroprotection and/or cognition enhancement in the subject. An effective amount of the therapeutic compound necessary to achieve a therapeutic effect may vary according to factors such as the amount of neurodegeneration that has already occurred at the clinical site in the subject, the age, sex, and weight of the subject, and the ability of the therapeutic compound to mitigate neurodegeneration and/or to effect neuroprotection and/or cognition enhancement in the subject. Dosage regimens can be adjusted to provide the optimum therapeutic response.

For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A non-limiting example of an effective dose range for a therapeutic compound of the invention (e.g., Va) is between 0.5 and 500 mg/kg of body weight per day. In an aqueous composition, preferred concentrations for the active compound (i.e., the therapeutic compound that can mitigate neurodegeneration and /or effect neuroprotection and /or cognition enhancement) are between 5 and 500 mM, more preferably between 10 and 100 mM, and still more preferably between 20 and 50 mM.

The therapeutic compounds of the invention can be effective when administered orally. Accordingly, a preferred route of administration is oral administration. Alternatively, the active compound may be administered by other suitable routes such as transdermal, subcutaneous, intraocular, intravenous, intramuscular or intraperitoneal administration, and the like (e.g., by injection). Depending on the route of administration, the active compound may be coated in a material to protect the compound from the action of acids, enzymes and other natural conditions which may inactivate the compound.

The compounds of the invention can be formulated to ensure proper distribution *in vivo*. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the therapeutic compounds of the invention cross the BBB, they

can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, e.g., U.S. Patents 4,522,811; 5,374,548; and 5,399,331. The liposomes may comprise one or more moieties which are selectively transported into specific cells or organs ("targeting moieties"), thus providing targeted drug delivery (see, e.g., Ranade et al., 1989).
5 Exemplary targeting moieties include folate and biotin (see, e.g., U.S. Patent 5,416,016 to Low et al.); mannosides (Umezawa et al., 1988); antibodies (Bloeman et al., 1995; Owais et al., 1995); and surfactant protein A receptor (Briscoe et al., 1995). In a preferred embodiment, the therapeutic compounds of the invention are formulated in liposomes; in a more preferred embodiment, the liposomes include a targeting moiety.

10

Delivery and *in vivo* distribution can also be affected by alteration of an anionic group of compounds of the invention. For example, anionic groups such as phosphonate or carboxylate can be esterified to provide compounds with desirable pharmacokinetic, pharmacodynamic, biodistributive, or other properties. Exemplary compounds include
15 IVI and pharmaceutically acceptable salts or esters thereof.

To administer the therapeutic compound by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the therapeutic compound may be
20 administered to a subject in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan et al., 1984).

25 The therapeutic compound may also be administered parenterally (e.g., intramuscularly, intravenously, intraperitoneally, intraspinally, or intracerebrally). Dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Pharmaceutical compositions suitable for injectable use include
30 sterile aqueous solutions (where water soluble) or dispersions and sterile powders

for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The vehicle can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants.

10

Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In some cases, it will be preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

15

Sterile injectable solutions can be prepared by incorporating the therapeutic compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the therapeutic compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yield a powder of the active ingredient (i.e., the therapeutic compound) optionally plus any additional desired ingredient from a previously sterile-filtered solution thereof.

20

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The therapeutic compound can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The therapeutic compound and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the
5 therapeutic compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the therapeutic compound in the compositions and preparations may, of course, be varied. The amount of the therapeutic compound in such therapeutically useful compositions is such that a suitable dosage will be obtained.

10

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to
15 produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such a therapeutic compound for the treatment of neurological conditions in
20 subjects.

Therapeutic compositions can be administered in time-release or depot form, to obtain sustained release of the therapeutic compounds over time. The therapeutic compounds of the invention can also be administered transdermally (e.g., by providing the
25 therapeutic compound, with a suitable carrier, in patch form).

Active compounds are administered at a therapeutically effective dosage sufficient to mitigate neurodegeneration and/or to effect neuroprotection and/or cognition enhancement in a subject. A "therapeutically effective dosage" preferably mitigates
30 neurodegeneration by about 20%, more preferably by about 40%, even more preferably by about 60%, and still more

preferably by about 80% relative to untreated subjects. The ability of a compound to mitigate neurodegeneration can be evaluated in model systems that may be predictive of efficacy in mitigating neurodegeneration in human diseases, such as animal model systems known in the art (including, e.g., the method of transient middle cerebral artery occlusion in the rat) or by *in vitro* methods, (including, e.g., the assays described herein).

It will be appreciated that the ability of a compound of the invention to mitigate neurodegeneration will, in certain embodiments, be evaluated by observation of one or more symptoms or signs associated with neurodegeneration *in vivo*. Thus, for example, the ability of a compound to mitigate neurodegeneration may be associated with an observable improvement in a clinical manifestation of the underlying neurodegeneration-related disease state or condition, or a slowing or delay in progression of symptoms of the condition. Thus, monitoring of clinical manifestations of disease can be useful in evaluating the neurodegeneration-mitigating efficacy of a compound of the invention.

The method of the invention is useful for treating neurodegeneration associated with any disease in which neurodegeneration occurs. Clinically, neurodegeneration can be associated with conditions including but not limited to: stroke; Parkinson's disease; Alzheimer's disease; Huntington's disease; multiple sclerosis; amyotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism; alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma to the head; hypoglycemia; hypoxia; myocardial infarction; cerebral vascular occlusion; cerebral vascular hemorrhage; hemorrhage; environmental excitotoxins of plant; animal and marine origin; dementias of all type; trauma; drug-induced brain damage; and aging; or result from surgical procedures such as cardiac bypass.

Novel compounds according to the invention can be synthesized by methods set forth herein (see, e.g., Working Examples) or in our patents U.S. No. 5,807,847 and U.S. No. 5,883,122. Various compounds for use in the methods of the invention are commercially

available and/or can be synthesized by standard techniques. In general, nitrate esters can be prepared from the corresponding alcohol, oxirane or alkene by standard methods, that include: nitration of alcohols and oxiranes, mixed aqueous/organic solvents using mixtures of nitric and sulfuric acid and/or their salts, with temperature control (see Yang et al., 1996); nitration of alcohols and oxiranes in acetic anhydride using nitric acid or its salts with or without added acid catalyst, with temperature control (see, e.g., Louw et al., 1976); nitration of an alcohol with a nitronium salt, e.g. a tetrafluoroborate; nitration of an alkene with thallium nitrate in an appropriate solvent (see Ouellette et al., 1976).

10 The following Examples further illustrate the present invention and are not intended to be limiting in any respect. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the claims.

15

Working Examples

Example 1

Characterization of guanylyl cyclase activation

20 Activation of soluble guanylyl cyclase (GCase) by nitrates IIIIm, IVa, IVb, IVd, IVe, IVf, IVg, IVj, Va, Vb, and GTN was assayed employing partially purified enzyme freshly prepared from the 105,000g supernatant fraction of rat aorta homogenates, using the radioimmunoassay method described by Bennett et al. (1992), the disclosure of which is incorporated herein by reference. Dose-response curves were obtained for GCase activation by nitrates IVa, IVb, IVd, IVe, IVf, IVg, IVj, and GTN in the presence and absence of cysteine and dithiothretol (DTT; both 2mM). In all cases, data were normalized to the maximal GTN response carried out in identical GCase preparations. Experimental incubations were performed at 37°C for 10 min. The data from these curves are summarized in Figures 1-8, which give: concentrations of nitrates required to give a response equivalent to the maximal response seen for GTN+cysteine; the maximal response measured for each nitrate, and; where applicable, potency. The GCase assay data show that IVd activates GCase, with a

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submillimolar EC_{50} in the absence of any added thiol, in contrast to GTN which requires added cysteine (Figs 1,2). Compounds IVd and IVg also activate GCase in the presence of DTT in contrast to GTN (Figs 2,3). Activation of GCase by IVb was cysteine-dependent and the response was very low ($EC_{50} > 1\text{mM}$) (Fig. 4). Activation of GCase by compound
5 IVf was cysteine-dependent and much greater than that achieved by GTN (Fig. 5). Activation of GCase by compound IVe was very low under all conditions tested (Fig. 6). Activation of GCase by compounds IVj and IVa was cysteine-dependent and approximately equivalent to GTN (Figs. 7,8). Relative to GTN itself, a wide range of potencies was observed for the nitrate esters of the invention. No activation of GCase by
10 glycerol mononitrates was observed in this assay at the concentrations of nitrate employed.

To test for potential differences in GCase activation by nitrates, the effects of IIIm, IVh, Va, Vb, and GTN were assayed in brain and vascular tissue. IVh had no effect on GCase activity in either rat aorta or rat hippocampus (Fig. 9). IIIm had greater efficacy to
15 stimulate GCase activity compared to GTN in both rat aorta and rat hippocampus (Fig. 9). Vb was found to be equivalent to GTN in efficacy and potency for activation of GCase in both rat aorta and rat hippocampus (Fig. 10). Va was found to have greater efficacy, but equal potency, to GTN in rat aorta (Fig. 10a). In contrast, Va had greater efficacy and greater potency to stimulate GCase in rat hippocampus (Fig. 10b). These data illustrate
20 that nitrates have differential effects on GCase activation that are dependent on both structure of the compound and the tissue assayed for GCase activity, supporting the notion that neuroprotective and cardiovascular effects of nitrates are separable.

Example 2

25 Characterization of cyclic GMP accumulation

In order to extend the GCase data further, the effects of nitrates Va, IIIm, Vb, Vc, and IVk on cyclic GMP accumulation in intact isolated rat aorta were examined (Figs. 11,12). Thoracic aortic strips were prepared from male Sprague-Dawley rats (Charles-River, Canada) as described in McGuire et al. (1994) and Stewart et al. (1989), both
30 incorporated herein by

reference. Tissues were contracted submaximally with phenylephrine (0.1 μ M) and exposed to various concentrations of drug for 1 min. Cyclic GMP accumulation was determined using the radioimmunoassay method described by Bennett et al. (1992). At concentrations of 1 μ M and 10 μ M, GTN and IVk significantly increased cGMP accumulation (Figs. 11, 12). At a concentration of 1 μ M, Va, III_m, Vb, and Vc did not significantly increase cyclic GMP accumulation (Figs. 11a, 12a). At a concentration of 10 μ M, Va, Vb, and IVk significantly increased cyclic GMP accumulation, whereas III_m and Vc did not (Figs. 11b, 12b).

Sections of rat hippocampus (400 μ m) were prepared and incubated in oxygenated Krebs solution at 37°C. After a 60-min equilibration period, the brain slices were stimulated with different concentrations of Va or GTN for 3-min. Cyclic GMP accumulation was determined as described above for aortic strips. Figure 13 shows that Va causes a concentration-dependent increase in the tissue levels of cGMP in rat hippocampal brain slices *in vitro* and that, at high concentration (100 μ M), Va is more effective than GTN in elevating cGMP levels in hippocampal brain slices *in vitro*. These data are in very good agreement with the differential effects of Va and GTN on hippocampal GCase activity shown in Figure 10b.

Example 3

Characterization of relaxation of isolated blood vessels

In order to extend the GCase data, the relaxing effects of nitrates III_m, IV_c, IV_d, IV_f, IV_g, IV_h, IV_k, Va, Vb, and Vc on rat aortic tissue were examined. Thoracic aortic strips were prepared from male Sprague-Dawley rats (Charles-River, Canada) as described in McGuire et al. (1994), and Stewart et al. (1989). Tissues were contracted submaximally with phenylephrine (0.1 μ M) and exposed to various concentrations of nitrovasodilator to obtain concentration-response curves. In this intact tissue assay, all of the nitrates were observed to cause relaxation of the tissue with a maximal relaxant response equal to that obtained with GTN. However, the compounds differed in potency with EC₅₀ (effective concentration for 50% of the subjects) values of 7.87 nM, 94.3 nM, 6.59 μ M, 25.2 μ M, 11.0 μ M, and 0.203 μ M, for GTN and compounds Va, IV_d, IV_g, IV_f, and IV_c, respectively (Fig. 14). In another series

of experiments, the EC_{50} values for relaxation were 0.61 nM, 3.19 nM, 8.40 nM, 0.153 μ M, 0.437 μ M and 6.89 μ M for GTN, IVk, Vb, IIIIm, Vc, and IVh, respectively (Fig. 15). The EC_{50} value for a nitrosothiol (*tert*-butyl nitrosothiol, Fig.16) was 11.2 μ M. Compounds IVd and IVc were tested for their ability to cause vascular relaxation in tissues that had been made tolerant to the relaxant effect of GTN. GTN tolerance was induced by incubating tissues with high concentrations of GTN (0.5mM GTN for 30 min). Under these conditions, the maximal relaxant effects of IVd (Fig.17a) and IVc (Fig.17b) were not significantly different from their effects for untreated tissue. The EC_{50} for relaxation was increased approximately threefold, but the difference was not statistically significant.

Example 4

Characterization of blood pressure changes in the whole animal

To test for differential effects of nitrates on blood pressure responses, Va and GTN were injected into rats in which the abdominal aorta was cannulated for blood pressure recording. In the first experiment, Va and GTN were injected subcutaneously at a dose of 400 μ mol/kg body weight into conscious, freely moving animals. GTN caused a small and transient decrease in blood pressure in these animals, whereas Va had no discernable effect on arterial blood pressure (Fig. 18). Va and GTN were subsequently tested in anesthetized rats in which the abdominal vena cava was also cannulated to allow for bolus intravenous injection of drugs. In this preparation, GTN caused a substantial and dose-dependent decrease in arterial blood pressure. In contrast, Va at equal doses had very modest effects on blood pressure at doses lower than 2 μ mol/kg body weight (Fig. 19). These data are in very good agreement with the results obtained for these two agents using the isolated blood vessel preparation.

The plasma levels of nitrates Vb and Vc (the denitrated metabolite of Vb) were measured to gain insight into the handling of these molecules in the body. Cannulas were placed in the abdominal aorta for blood sampling. After a two-day recovery period, a single subcutaneous dose of Vb (200 μ mol/kg) was administered and blood samples collected over a period of six hours. Samples were centrifuged, the plasma collected, and the concentrations of

Vb and Vc determined by gas-liquid chromatography by the method of McDonald and Bennett (1990). The data obtained for Vb and Vc indicate that nitrates achieve maximal plasma levels within 30 minutes after subcutaneous injection, and thereafter decline at a steady rate (Fig. 20). These data suggest that nitrates have excellent bioavailability after subcutaneous injection.

Example 5

Characterization of neuroprotection in brain slices

In order to test for potential neuroprotective properties, the effects of Va were tested in an *in vitro* model of cerebral ischemia. Rat hippocampal slices were subjected to 30 minutes of ischemia by incubation in a buffered salt solution lacking glucose and oxygen. Sections of rat hippocampus (400 μ m) were prepared and incubated in oxygenated Krebs solution at 37°C. Slices were then either untreated or subjected to a 30-minute period of ischemia by incubation in Krebs solution lacking oxygen and glucose. Slices were then incubated for a further 4 hours in oxygenated Krebs solution in the presence of drug vehicle or 200 μ M Va. At the end of the 4-hr re-oxygenation period, release of the cytosolic enzyme lactate dehydrogenase (LDH) from the tissue was used as an index of neuronal cell injury. Some hippocampal slices were treated with Va (200 μ M) after the 30-minute period of ischemia. Figure 21 shows that Va significantly reduced the release of LDH from ischemic brain slices when administered immediately after the period of ischemia. Figure 22 shows that Va was still effective at protecting ischemic brain slices *in vitro* when drug exposure was delayed for up to 1 hour after re-oxygenation of the tissue.

To test the mechanism of this neuroprotection, rat hippocampal brain slices made ischemic for 30 minutes *in vitro* were exposed to the guanylyl cyclase inhibitor ODQ 5-min prior to administration of 200 μ M Va. The concentration of ODQ used was known to completely block the production of cGMP induced by Va. Blockade of guanylyl cyclase by ODQ completely eliminated the neuroprotective effect of Va in ischemic rat hippocampal

slices, showing that elevations in cGMP levels are directly related to the neuroprotective properties of Va *in vitro* (Fig. 23).

Example 6

5 Characterization of neuroprotection in the whole animal

To test the efficacy of nitrates in animal models of cerebral ischemia, two different approaches were taken. In the first, Mongolian gerbils were subjected to 5 minutes of global forebrain ischemia by occlusion of the common carotid arteries under halothane anesthesia. This period of ischemia produces a selective neuronal cell death in the CA1
10 region of the hippocampus that develops over several days. Surgical procedures, and control of brain and body temperature during the occlusion, were as described in Nurse and Corbett (1996), incorporated herein by reference. Animals were given two subcutaneous injections of drug vehicle, or 400 $\mu\text{mol/kg}$ IVh, Vb or Va at 5-min and 90-min after the occlusion. Sham-treated animals had the carotid arteries exposed but not
15 occluded. Seven days later, the brains were fixed by transcardiac perfusion with 4% paraformaldehyde, dissected out, embedded in paraffin, and 5 μm sections were cut and stained with cresyl violet. Viable neurons in 100 square μm blocks of the CA1 region were counted to obtain an index of neuronal cell damage. The results obtained with nitrates IVh, Vb, and Va are shown in Figure 24. Both Va and Vb produced a statistically
20 significant neuroprotection against 5 minutes of global forebrain ischemia in the gerbil.

The second animal model tested was transient focal cerebral ischemia in the rat induced by occlusion of the middle cerebral artery. Under halothane anesthesia, a filament was advanced into the right internal carotid artery until the origin of the right middle
25 cerebral artery was occluded. The filament was secured, the animal allowed to regain consciousness, and two hours later the filament was removed under halothane anesthesia. Animals were given five subcutaneous doses of drug vehicle or 200 $\mu\text{mol/kg}$ Va at 2, 3, 4, 6, and 8 hr post-occlusion. At 24 hr post-occlusion the animals were sacrificed, the brain removed, cut into 2-mm coronal sections and stained for viable tissue with 2,3,5-
30 triphenyltetrazolium. Infarct

volume of whole brain and cerebral cortex was quantitated by computer-assisted image analysis. A 2-hour episode of cerebral ischemia followed by recirculation produces a large infarct in the cerebral cortex and subcortical structures on the affected side. The volumes of the total and cerebral cortical infarct in the rat brain were very similar to those reported by other groups using the same procedure (e.g., Sydserff et al., 1995; Morikawa et al., 1998). Figure 25 shows the results obtained with nitrate Va in this model. A series of subcutaneous injections of Va at a dose of 200 μ mol/kg body weight at 2, 3, 4, 6, and 8 hours after the onset of cerebral ischemia resulted in a statistically significant neuroprotection when assayed 24 hours after ischemia. Collectively, these data indicate that delayed administration of Va is neuroprotective in two different animal models of cerebral ischemia.

In a separate series of experiments, the effects of organic nitrates on focal excitotoxic lesions induced by localized application of NMDA in the rat brain were determined. Male Sprague-Dawley rats were stereotactically infused with NMDA into the right substantia nigra as described in Connop et al. (1995), incorporated herein by reference. Four days later, both striata were dissected and assayed for tyrosine hydroxylase (TH) activity. Loss of TH activity in the striata is a quantitative index of NMDA-induced neuronal cell death in the substantia nigra. The striata of each animal were compared to express neurotoxicity as a percent decrease in TH activity of the ipsilateral striatum as compared to the contralateral striatum. Pretreatment of these animals with GTN (administered as a subcutaneous patch inserted under halothane anesthesia one hour prior to the NMDA infusion) at doses of 0.2 and 0.4 mg/hr produced a dose-dependent reduction in the loss of TH activity from the ipsilateral striatum (Fig. 26). Figure 27 shows that delaying the administration of GTN until one hour after the NMDA infusion was equally effective at preventing NMDA-induced neuronal cell death in the substantia nigra. Losartan, a drug that decreases systemic blood pressure through a mechanism different from that of GTN, had no neuroprotective effects (Fig. 28). This shows that any vasorelaxation caused by GTN is not the mechanism of the neuroprotection against excitotoxic cell death induced by NMDA. Figure 29 shows that the doses of losartan and GTN used in these studies caused an equivalent decrease in systemic blood pressure. Male

Sprague-Dawley rats with aortic catheters were connected to pressure transducers which recorded blood pressure for 4 to 8 hours. The animals treated with subcutaneous 0.4 mg/hour GTN patches implanted in the dorsal neck region, showed a 15% decrease in MAP 250 minutes post implantation. Animals treated with a single 30 mg/kg intraperitoneal injection of Losartan showed a 20% decrease in MAP 250 minutes after injection. From these data, treatment protocols for the NMDA infusion experiments shown in Figure 28 were generated.

Example 7

10 *Characterization of neuroreceptor interactions*

The direct effects of organic nitrates on amino acid neurotransmitter receptors has been tested using the *Xenopus* oocyte expression system and two-electrode voltage-clamp recording methods. Human recombinant γ -aminobutyric acid type A (GABA_A) receptors composed of $\alpha 1\beta 2\gamma 2L$ subunits were expressed in *Xenopus* oocytes as described in Reynolds et al. (1996), incorporated herein by reference. GABA_A receptor-activated membrane current was recorded in individual oocytes, and modulation of this current by GTN and organic nitrates described herein was assessed. GABA (10 μ M) was applied until the peak steady-state current response was obtained. IVd (Bunte salt) was pre-applied for 30 seconds prior to exposure of the oocyte to GABA. At 100 μ M, IVd produced a 55% inhibition of the response to 10 μ M GABA (Fig. 30). This effect appears to be unrelated to the production or release of nitric oxide, as diethylamine nonoate salt (DEA) and *t*-butylnitrosothiol (*t*-BuSNO) which both spontaneously release nitric oxide in aqueous solution, had no effect on GABA receptor-activated membrane current in an oocyte expressing the $\alpha 1\beta 2\gamma 2L$ isoform of the GABA_A receptor. In contrast, nitroglycerin (GTN) produced a reversible inhibition of the GABA response (Fig. 31). Organic nitrates such as GTN and IVd do not compete with GABA for binding to the GABA_A receptor. Rather, they are believed to produce an allosteric modulation of the receptor that decreases the maximal current without changing the apparent affinity of the receptor for GABA. For example, compound IVd (Bunte salt, pre-applied for 30 seconds) decreased the peak current amplitude in an oocyte from 302 nA to 150 nA. However, the EC₅₀ concentration (GABA concentration producing 50% of the maximal

response) for GABA was not changed (Fig. 32). Other organic nitrates described herein have been found to have similar inhibitory effects on GABA_A receptor-activated membrane current.

5 *Example 8*

Synthesis of IIIe

To acetic anhydride (3 mL) was added gradually, with stirring, 70% nitric acid (0.26 mL), while keeping the temperature between 20-30° by external cooling. With continuous vigorous stirring the mixture was cooled to -30-35° and 2',3'-dideoxy-3-thiocytosine (0.25 g) was added. After 10 min. at -35°, the reaction mixture was heated up to -20° and then stirred at -20-10° for 15 min, and 10 min. at 0°. The resulting reaction mixture was poured into ice-water, stirred for 1 hr, then NaHCO₃ was added by portions until CO₂ evolution ceased. The water solution was extracted with 3x20 mL of ethyl acetate. Combined extracts were dried (MgSO₄) and concentrated. 0.38 g of slightly yellowish oil was obtained. The oil crystallized in a day and was recrystallized from CHCl₃. Yield 52%. Conversion to the nitrate was evidenced by the significant downfield shift of the C5' proton multiplet from δ 3.6 to 4.85 ppm.

Example 9

20 *Synthesis of nitrate IIIf*

0.26 mL (4.15 mmol) conc. HNO₃ was added to 2 mL acetic anhydride such that the temperature did not exceed 25 - 30 °C. The mixture was cooled at 0 - 5 °C and 0.3 g (1.88 mmol) of 5-(1,2-dihydroxyethyl)-4-methylthiazole was added in several portions, the temperature being kept below 5 °C. The reaction mixture was stirred at 0 - 5 °C for 45 min and then 0.45 mL water was added. The mixture was stirred for 30 min and then rotary evaporated. The residue was neutralized by adding 5 mL of saturated NaHCO₃ solution and the organic product was extracted with ethyl acetate. The organic layer was concentrated and the dinitrate IIIf was purified through column chromatography (silica gel/ ethyl acetate eluant). A slightly yellow solid was obtained. Yield: 0.150 g (32 %).

*Example 10**Synthesis of nitrate IIIi*

Nitrate IIIi was obtained by two routes. Route I proceeded from the elimination reaction of IIIm in basic solution. Route II proceeded from nitration of *trans*-3-bromo-4-hydroxytetrahydrothiophene-1,1-dioxide, yielding nitrate IIIn, followed by reaction with a weak base, e.g., sodium thiocyanate in 2-butanone. Purification is achieved with silica flash column chromatography using 1:1 hexane:ethyl acetate as eluant.

*Example 11**Synthesis of nitrate IIIj*

1,4-Dibromo-2,3-butanediol is nitrated: (a) using a nitration mixture prepared from HNO₃ and H₂SO₄ over 2 days; or (b) using acetyl nitrate reacting for 2 hours. Work-up requires quenching of the reaction mixture in ice-water for an hour, extraction, drying, and evaporation. Successful purification of the title compound by silica gel column chromatography is achieved on a 25 g scale using a mixture of 70% hexane and 30% CH₂Cl₂ as eluent.

*Example 12**Synthesis of nitrate IIIk and IIIl*

Synthesis from dinitrate IIIj proceeded by refluxing with sodium or potassium thiocyanate (2 eq.) in 2-butanone for 8 hr. After cooling, a precipitate was removed by filtration and the filtrate was concentrated. Nitrates IIIk and IIIl were separated by silica flash column chromatography with hexane/dichloromethane as eluent.

*Example 13**Synthesis of nitrate IIIm*

3,4-Epoxytetrahydrothiophene-1,1-dioxide (250 mg, 1.9 mmol) was refluxed for 24 hrs in 10 mL of water and 25mg of toluenesulfonic acid. After the first 6 hrs, another 25 mg of

the acid was added. The reaction was monitored by thin layer chromatography (5% MeOH in dichloromethane). Purification was by silica flash column chromatography using 5% MeOH/CH₂Cl₂ as eluent to afford 200 mg of diol. The diol was nitrated in a cooled solution of conc. sulfuric acid (2 mol eq.), nitric acid (70%, 2 mol eq.) in an ice bath.

5 The temperature was maintained as close to 0 °C as possible. The ice bath was removed and the mixture was allowed to stir for 1 hour (reaction was monitored by thin layer chromatography, 100% CH₂Cl₂ eluent). The acid layer was removed and the organic layer washed with: (i) water; (ii) 10% sodium carbonate; (iii) 10% urea; (iv) water. Drying over sodium sulfate, filtration and concentration, yielded crude product which was purified by

10 flash column chromatography, with dichloromethane as eluent. An alternative route involves direct nitration of 3,4-epoxytetrahydrothiophene-1,1-dioxide in a similar nitration mixture.

Example 14

15 *Synthesis of nitrate IVk*

1.17 mL (18.2 mmol) concentrated HNO₃ was added, under stirring and cooling (0 – 5 °C), to 1 mL (18.2 mmol) concentrated H₂SO₄ and then 2 g (14 mmol) of 4-methyl-5-(2-hydroxyethyl)thiazole was added dropwise into the nitration mixture, the temperature being kept under 10 °C. The mixture was stirred for 3 hours at room temperature, diluted

20 with 10 mL of water and neutralized with solid NaHCO₃. The organic product was extracted with ethyl acetate and purified by column chromatography (silica gel/ ethyl acetate eluant) to produce a colorless oily product. Yield: 1.18 g (45%).

Example 15

25 *Synthesis of nitrate Ivi*

0.03 g (0.035 ml) of allyl cyanide was added to a stirred suspension of 0.22 g (0.5 mmol) of Tl (NO₃)₃·3H₂O in 2 mL of pentane. After 20 min of vigorous stirring, the pentane solution was decanted and evaporated to dryness. After evaporation the residual oil (0.44 g) was

columned (CH₂Cl₂, R_f 0.64 (CH₂Cl₂). Clean oil immediately crystallized during an attempt to

30 dissolve it in CDCl₃. Yield 0.065 g (76%). The structure of IVn was confirmed by

X-ray analysis. IR (film): 1297.03, 1678.91, 2258.91 (CN). Mass spec. m/z (CI^+ fragment, %): 191.9 ($M+H$, 2.44), 129.0 (16.41), 81.9 (100). Calculated for $C_4H_5N_3O_6$ 191.02.

Example 16

5 *Synthesis of nitrate IVn*

0.9 g (0.75 mL, 4.92 mmol) of allylphenyl sulfone was added dropwise to a stirred suspension of 2.43 g (5.47 mmol) of $Tl(NO_3)_3 \cdot 3H_2O$ in 10 mL of pentane. The resulting mixture was stirred overnight. The pentane solution was decanted. 2x10 mL of MeOH (methanol) were added to the reaction mixture, stirred for 10 minutes and extracts were
10 added to the pentane solution. The combined extracts were evaporated to dryness and purified by silica flash column chromatography using CH_2Cl_2 as eluant. Yield 0.08 g (15%). IR (KBr): 1152.39, 1290.91, 1273.12, 1353.83, 1646.08. Mass spec. m/z (CI^+ fragment, %): 307.0 ($M+1$, 66.5), 244.0 (100%). Calculated for $C_9H_{10}N_2O_8S$ 306.02.

15 *Example 17*

Synthesis of nitrate Va

2.2 g (7.3 mmol) of nitrate IVd was dissolved in 5 g of cold H_2O_2 (30%, 0°C) and then 1 g of 10 % H_2SO_4 was added. The mixture was stirred at 0-5 °C until a white oil separated (ca. 30-60 min). The aqueous layer was discarded and the oil was dissolved in
20 dichloromethane, washed successively with water, then $NaHCO_3$ solution and finally water. The organic solution was dried over $MgSO_4$. Removal of the solvent produced 1.3 g of the crude product which was purified by column chromatography (Silicagel, CH_2Cl_2 /hexanes : 70/30). Yield: 0.650 g (45 %).

25 *Example 18*

Synthesis of nitrate Vc.

3 g (8.88 mmol) of 1,4-dibromo-2,3-dinitrobutanediol and 2.81 g (18 mmol) of $Na_2S_2O_3 \cdot 5H_2O$ were dissolved in a mixture of 100 mL of MeOH and 45 mL of H_2O . The resulting solution was heated during 4 days at 40-45°. After this time the reaction mixture was

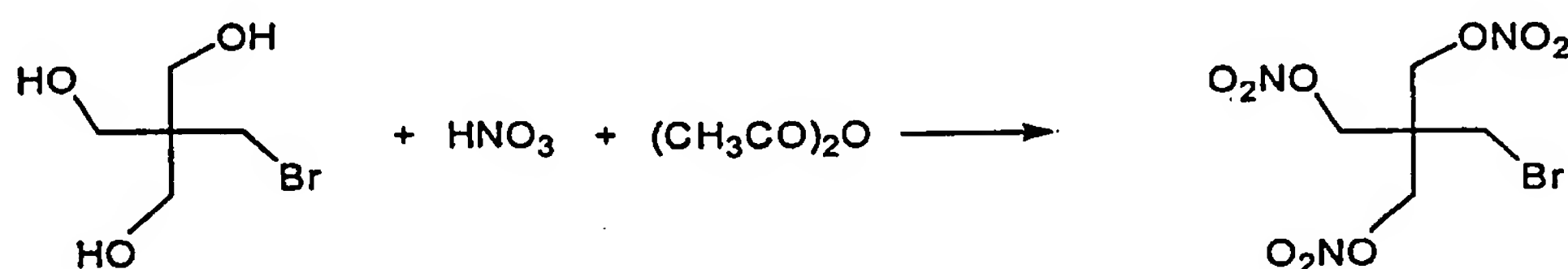
partially evaporated to reduce the volume of solvents. The resulting mixture was extracted 4x50 mL of ethyl ether. The extracts were combined, washed (H₂O), dried (MgSO₄) and evaporated to minimum. Column chromatography afforded the title compound in 10% yield, separated from Vb, the major product.

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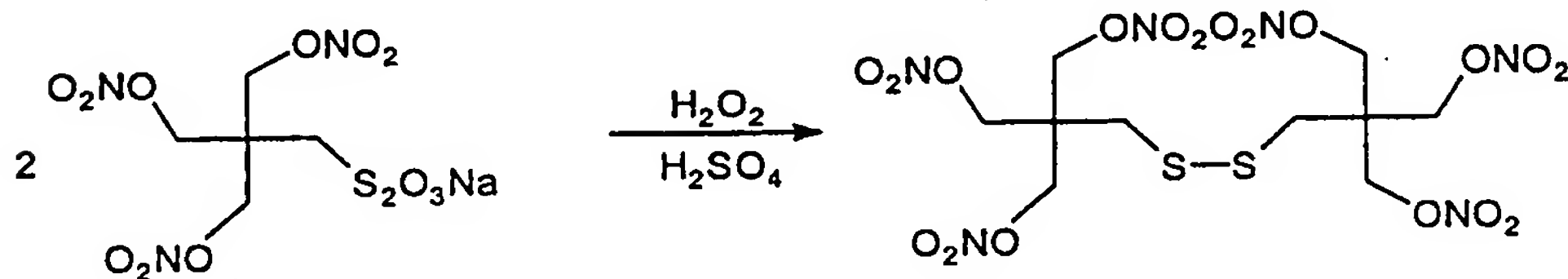
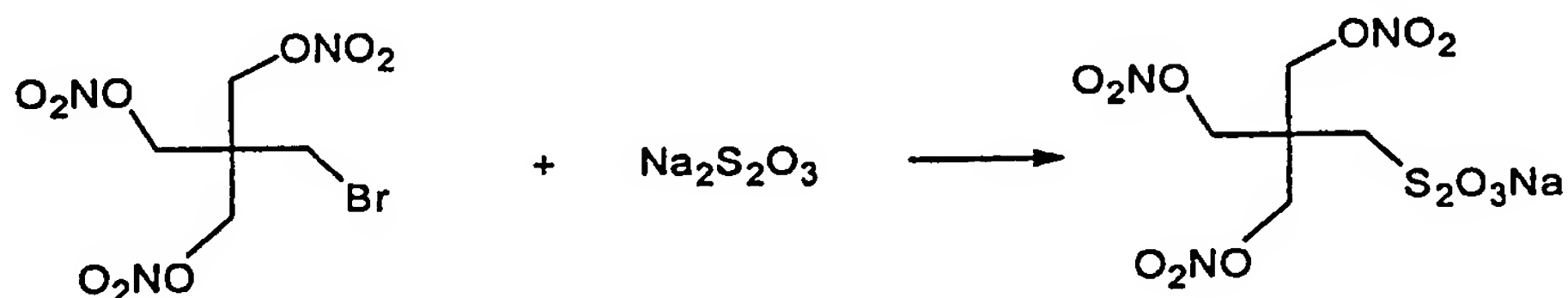
*Example 19**Synthesis of nitrate IIIh*

The synthetic route employed for synthesis of the hexanitrate IIIh is shown in the Scheme:

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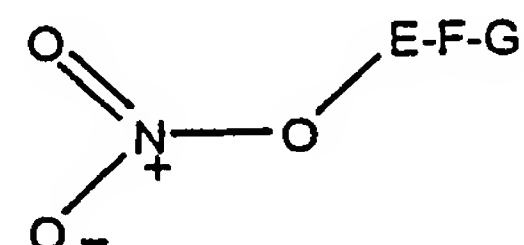
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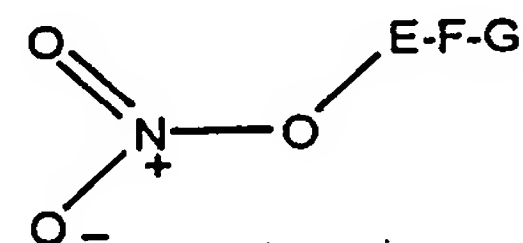
What is claimed is:

1. A method for effecting cognition enhancement in a subject in need thereof comprising administering to said subject an effective amount of a therapeutic compound such that cognition enhancement occurs, wherein the therapeutic compound has the formula (Formula I):



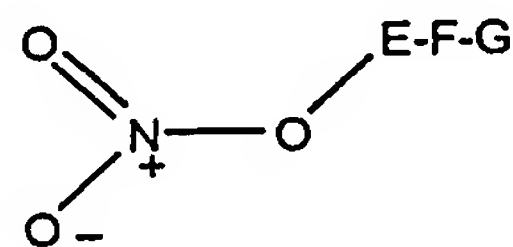
wherein E, F, G are organic radicals which may contain inorganic counterions.

2. A method for mitigating cellular damage due to ischemia in a subject in need thereof comprising administering to said subject an effective amount of a therapeutic compound such that cellular damage is mitigated, wherein the therapeutic compound has the formula (Formula I):



wherein E, F, G are organic radicals which may contain inorganic counterions.

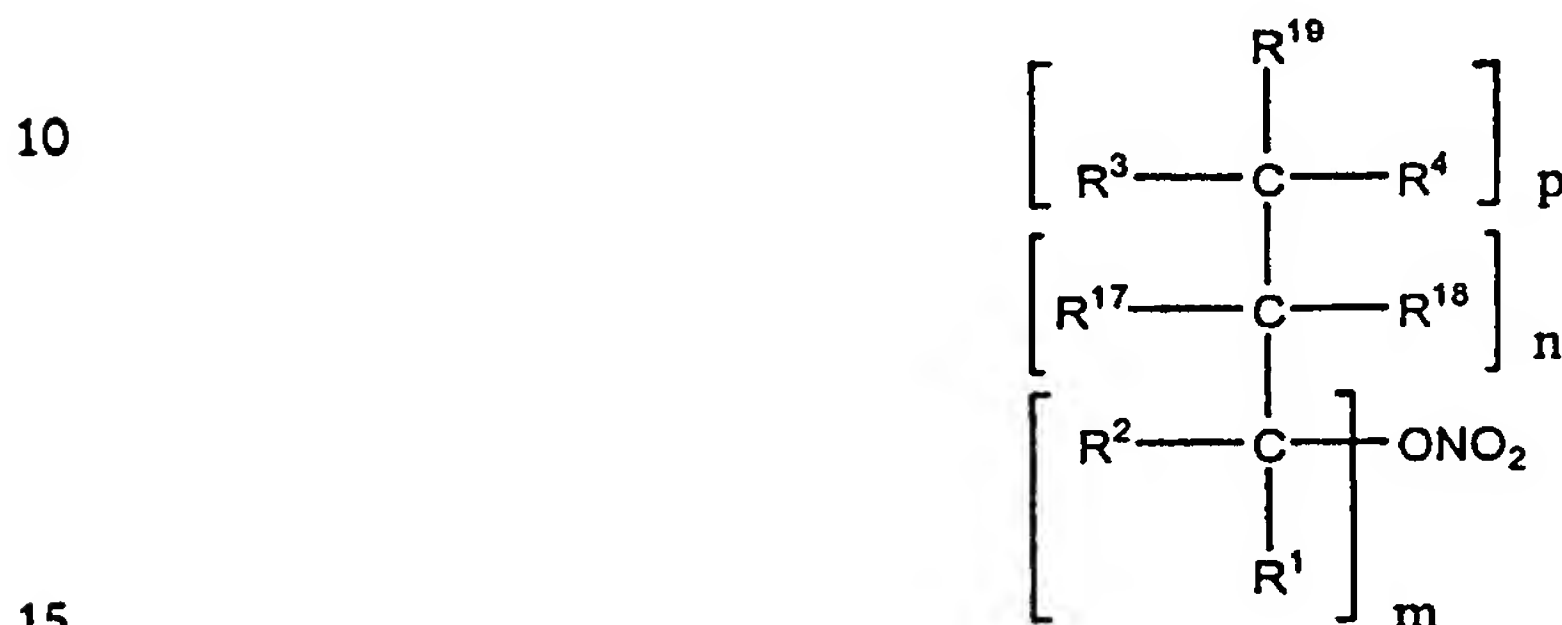
3. A method for mitigating neurodegeneration in a subject, comprising administering to said subject an effective amount of a therapeutic compound such that mitigation of neurodegeneration occurs, wherein the therapeutic compound has the formula (Formula I):



wherein E, F, G are organic radicals which may contain inorganic counterions,

with the proviso that when E is methylene, F and G are not both C₁ organic radicals each bearing one nitrate group.

4. A method for mitigating neurodegeneration in a subject, comprising administering to said subject an effective amount of a therapeutic compound such that mitigation of neurodegeneration occurs, wherein the therapeutic compound has the formula (Formula II):



in which: m, n, p are integers from 0 to 10;

R^{3,17} are each independently hydrogen, a nitrate group, or A;

R^{1,4} are each independently hydrogen or A;

- 20 where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR⁶ and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R¹ and R³ and/or between R¹⁷ and R⁴, which optionally contains O, S, NR⁶ and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a

substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R², R⁵, R¹⁸, R¹⁹ are optionally hydrogen, A, or X-Y;

10 where X is F, Br, Cl, NO₂, CH₂, CF₂, O, NH, NMe, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³), PO₂H, PO₂M, P(O)(OR¹⁴),
15 P(O)(R¹³), SO, SO₂, C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵;

Y is F, Br, Cl, CH₃, CF₂H, CF₃, OH, NH₂, NHR⁶, NR⁶R⁷, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M,
20 CO₂H, CO₂R¹¹, C(O)R¹², C(O)(OR¹³), C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵, or does not exist;

R⁶, R⁷, R⁸, R⁹, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO₂ substituents; or C₁ - C₆ connections to R¹ - R⁴ in cyclic derivatives; or are each independently hydrogen, a nitrate group, or A; and

25 M is H, Na⁺, K⁺, NH₄⁺, N⁺H_kR¹¹_(+k) where k is 0-3, or other pharmaceutically acceptable counterion;
and with the proviso,

when m = n = p = 1; R¹⁹, R², R¹⁸, R¹ = H; R¹⁷, R³ are nitrate groups;
that R⁴ is not H or C₁ - C₃ alkyl.

5. The method of claim 4, wherein:

R^{19} is X-Y.

5 6. The method of claim 5, wherein:

R^1 and R^3 are the same or different and selected from H, C_1 - C_4 alkyl chains, which may include one O, linking R^1 and R^3 to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which rings optionally bear hydroxyl substituents;

R^2 and R^4 , are the same or different and selected from H, a nitrate group, C_1 - C_4 alkyl optionally bearing 1-3 nitrate group, and acyl groups ($-C(O)R^5$);

R^7 , R^{11} are the same or different $C_1 - C_8$, alkyl or acyl;

R^5 , R^6 , R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 or C_2 connections to $R^1 - R^3$ in cyclic derivatives; and

15 M is H, Na^+ , K^+ , NH_4^+ , $N^+H_kR^{11}_{(4-k)}$ where k is 0-3.

7. The method of claim 6, wherein:

$m = 1$, $n = 0$, $p = 1$.

20 8. The method of claim 7, wherein:

X is CH_2 , O, NH, NMe, CN, NHOH, N_2H_3 , $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3 , S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SH, SR^7 , SO_2M , $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3HM , PO_3M_2 , $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M , CO_2H , CO_2R^{11} , $C(O)$, $C(O)R^{12}$, $C(O)(OR^{13})$,

25 PO_2M , $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2 , $C(O)(SR^{13})$, SSR^4 ; and

Y is CN, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3 , SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SR^4 , SO_2M , PO_3HM , PO_3M_2 , $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M , CO_2H , CO_2R^{11} , $C(O)R^{12}$, $C(O)(SR^{13})$, SR^5 , SSR^5 , or does not exist.

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9. The method of claim 6, wherein:

$R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$ are the same or different alkyls containing 1-12 carbon atoms; or C_1 or C_2 connections to R^1 or R^3 in cyclic derivatives;

X is $CH_2, O, NH, NMe, S, SO_3M, SH, SR^7, SO_2M, S(O)R^8, S(O)_2R^9, S(O)OR^8, S(O)_2OR^9, PO_3M_2, P(O)(OR^{15})(OR^{16}), P(O)(OR^{16})(OM), P(O)(R^{15})(OR^8), PO_3HM$ or
5 $P(O)(OM)R^{15}$; and

Y is $SO_2M, SO_3M, PO_3HM, PO_3M_2, P(O)(OR^{15})(OR^{16}), P(O)(OR^{16})(OM), SR^5, SR^4$ or SSR^5 , or does not exist.

10 10. The method of claim 3, wherein the therapeutic compound is administered orally, intravenously, buccally, transdermally or subcutaneously.

11. The method of claim 3, further comprising administering the therapeutic compound in a pharmaceutically acceptable vehicle.

15 12. The method of claim 3, wherein administering the therapeutic compound to the subject modulates an activity of the glutamate neuroreceptor.

13. The method of claim 3, wherein administering the therapeutic compound to the subject modulates an activity of a non-glutamate neuroreceptor.

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14. The method of claim 3, wherein administering the therapeutic compound to the subject modulates cerebral guanylyl cyclase activity.

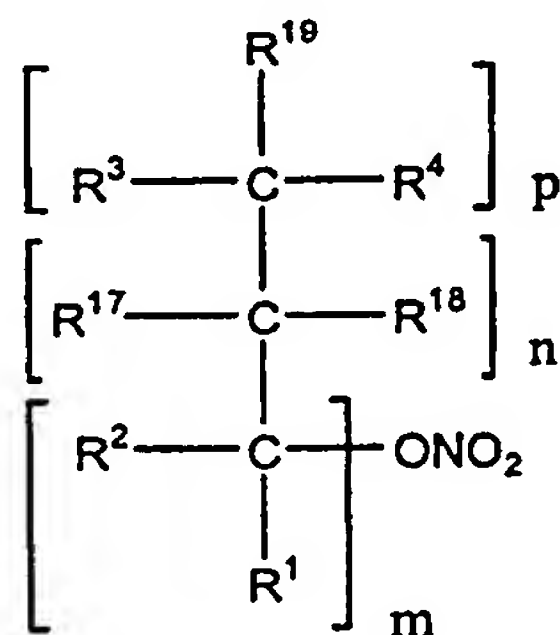
25 15. The method of claim 3, wherein administering the therapeutic compound to the subject modulates apoptosis.

16. The method of claim 3, wherein administering the therapeutic compound to the subject modulates cerebral free radical damage.

17. A method for treating a disease state associated with neurodegeneration in a subject, comprising administering to said subject an effective amount of a therapeutic compound such that a disease state associated with neurodegeneration is treated, wherein the therapeutic compound has the formula (Formula II):

5

10



in which: m, n, p are integers from 0 to 10;

15

$R^{3,17}$ are each independently hydrogen, a nitrate group, or A;

$R^{1,4}$ are each independently hydrogen or A;

20

where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR^6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R^1 and R^3 and/or between R^{17} and R^4 , which optionally contains O, S, NR^6 and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages

25

(e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties),
 5 arylamino, diarylamino, and alkylaryl amino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R², R⁵, R¹⁸, R¹⁹ are optionally hydrogen, A, or X-Y;

where X is F, Br, Cl, NO₂, CH₂, CF₂, O, NH, NMe, CN, NHOH, N₂H₃,
 N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂,
 10 SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM,
 PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵,
 CO₂M, CO₂H, CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³), PO₂H, PO₂M, P(O)(OR¹⁴),
 P(O)(R¹³), SO, SO₂, C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵;

Y is F, Br, Cl, CH₃, CF₂H, CF₃, OH, NH₂, NHR⁶, NR⁶R⁷, CN, NHOH, N₂H₃,
 15 N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂,
 SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM,
 PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M,
 CO₂H, CO₂R¹¹, C(O)R¹², C(O)(OR¹³), C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵, or does not exist;

R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ are the same or different alkyl or acyl
 20 groups containing 1-24 carbon atoms which may contain 1-4 ONO₂ substituents; or C₁ -
 C₆ connections to R¹ - R⁴ in cyclic derivatives; or are each independently hydrogen, a
 nitrate group, or W; and

M is H, Na⁺, K⁺, NH₄⁺, N⁺H_kR¹¹_(4-k) where k is 0-3, or other pharmaceutically
 acceptable counterion;

25 and with the proviso,

when m = n = p = 1; R¹⁹, R², R¹⁸, R¹ = H; R¹⁷, R³ are nitrate groups;
 that R⁴ is not H or C₁ - C₃ alkyl.

18. The method of claim 17, wherein:

30 R¹⁹ is X-Y.

19. The method of claim 18, wherein:

R^1 and R^3 are the same or different and selected from H, C_1 - C_4 alkyl chains, which may include one O, linking R^1 and R^3 to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which rings optionally bear hydroxyl substituents;

5 R^2 and R^4 , are the same or different and selected from H, a nitrate group, C_1 - C_4 alkyl optionally bearing 1-3 nitrate group, and acyl groups ($-C(O)R^5$);

R^7 , R^{11} are the same or different C_1 - C_8 , alkyl or acyl;

R^5 , R^6 , R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 or C_2 connections to R^1 - R^3 in cyclic derivatives; and

10 M is H, Na^+ , K^+ , NH_4^+ , $N^+H_kR^{11}_{(4-k)}$ where k is 0-3.

20. The method of claim 19, wherein:

$m = 1$, $n = 0$, $p = 1$.

15

21. The method of claim 20, wherein:

X is CH_2 , O, NH, NMe, CN, NHOH, N_2H_3 , $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3 , S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SH, SR^7 , SO_2M , $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3HM , PO_3M_2 , $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$,
20 $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M , CO_2H , CO_2R^{11} , $C(O)$, $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2M , $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2 , $C(O)(SR^{13})$, SSR^4 ; and

Y is CN, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3 , SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SR^4 , SO_2M , PO_3HM , PO_3M_2 , $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M , CO_2H , CO_2R^{11} , $C(O)R^{12}$, $C(O)(SR^{13})$, SR^5 , SSR^5 , or
25 does not exist.

22. The method of claim 20, wherein:

R^5 , R^6 , R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} are the same or different alkyls containing 1-12 carbon atoms; or C_1 or C_2 connections to R^1 or R^3 in cyclic derivatives;

X is CH₂, O, NH, NMe, S, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), PO₃HM or P(O)(OM)R¹⁵; and

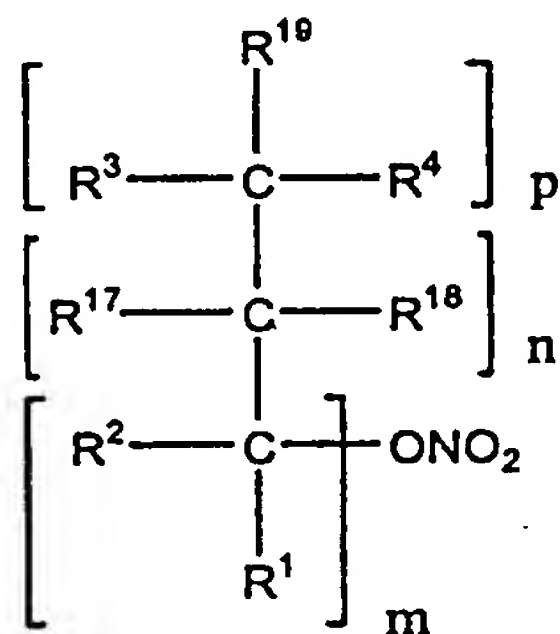
Y is SO₂M, SO₃M, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), SR⁵, SR⁴ or SSR⁵, or does not exist.

23. The method of claim 2, wherein administering the therapeutic compound to the subject modulates levels of cyclic nucleotide cGMP and/or cAMP.

24. The method of claim 17, wherein the therapeutic compound is administered orally, intravenously, buccally, transdermally or subcutaneously.

25. The method of claim 17 further comprising administering the therapeutic compound in a pharmaceutically acceptable vehicle.

26. A method for effecting neuroprotection in a subject, comprising administering to said subject an effective amount of a therapeutic compound such that neuroprotection occurs, wherein the therapeutic compound has the formula (Formula II):



in which: m, n and p are integers from 0 to 10;

R^{3,17} are each independently hydrogen, a nitrate group, or A;

R^{1,4} are each independently hydrogen or A;

where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR⁶ and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R¹ and R³ and/or between R¹⁷ and R⁴, which optionally contains O, S, NR⁶ and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R², R⁵, R¹⁸, R¹⁹ are optionally hydrogen, A, or X-Y;

where X is F, Br, Cl, NO₂, CH₂, CF₂, O, NH, NMe, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³), PO₂H, PO₂M, P(O)(OR¹⁴), P(O)(R¹³), SO, SO₂, C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵;

Y is F, Br, Cl, CH₃, CF₂H, CF₃, OH, NH₂, NHR⁶, NR⁶R⁷, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O)R¹², C(O)(OR¹³), C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵, or does not exist;

$R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents; or $C_1 - C_6$ connections to $R^1 - R^4$ in cyclic derivatives; or are each independently hydrogen, a nitrate group, or W; and

- 5 M is $H, Na^+, K^+, NH_4^+, N^+H_kR^{11}_{(+k)}$ where k is 0-3, or other pharmaceutically acceptable counterion;
and with the proviso,

when $m = n = p = 1$; $R^{19}, R^2, R^{18}, R^1 = H$; R^{17}, R^3 are nitrate groups;
that R^4 is not H or $C_1 - C_3$ alkyl.

10

27. The method of claim 26, wherein:

R^{19} is X-Y.

28. The method of claim 27, wherein:

- 15 R^1 and R^3 are the same or different and selected from H, $C_1 - C_4$ alkyl chains which may include one O, linking R^1 and R^3 to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which rings optionally bear hydroxyl substituents;

R^2 and R^4 are the same or different and selected from H, a nitrate group, $C_1 - C_4$ alkyl optionally bearing 1-3 nitrate group, and acyl groups $(-C(O)R^5)$;

- 20 R^7, R^{11} are the same or different $C_1 - C_8$ alkyl or acyl;

$R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$ are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 or C_2 connections to $R^1 - R^3$ in cyclic derivatives; and

M is $H, Na^+, K^+, NH_4^+, N^+H_kR^{11}_{(+k)}$ where k is 0-3.

25

29. The method of claim 28, wherein:

$m = 1, n = 0, p = 1$.

30. The method of claim 29, wherein:

X is CH_2 , O, NH, NMe, CN, NHOH, N_2H_3 , $\text{N}_2\text{H}_2\text{R}^{13}$, $\text{N}_2\text{HR}^{13}\text{R}^{14}$, N_3 , S, SCN, $\text{SCN}_2\text{H}_2(\text{R}^{15})_2$, $\text{SCN}_2\text{H}_3(\text{R}^{15})$, $\text{SC}(\text{O})\text{N}(\text{R}^{15})_2$, $\text{SC}(\text{O})\text{NHR}^{15}$, SO_3M , SH, SR^7 , SO_2M , $\text{S}(\text{O})\text{R}^8$, $\text{S}(\text{O})_2\text{R}^9$, $\text{S}(\text{O})\text{OR}^8$, $\text{S}(\text{O})_2\text{OR}^9$, PO_3HM , PO_3M_2 , $\text{P}(\text{O})(\text{OR}^{15})(\text{OR}^{16})$, $\text{P}(\text{O})(\text{OR}^{16})(\text{OM})$, $\text{P}(\text{O})(\text{R}^{15})(\text{OR}^8)$, $\text{P}(\text{O})(\text{OM})\text{R}^{15}$, CO_2M , CO_2H , CO_2R^{11} , $\text{C}(\text{O})$, $\text{C}(\text{O})\text{R}^{12}$, $\text{C}(\text{O})(\text{OR}^{13})$, PO_2M , $\text{P}(\text{O})(\text{OR}^{14})$, $\text{P}(\text{O})(\text{R}^{13})$, SO, SO_2 , $\text{C}(\text{O})(\text{SR}^{13})$, SSR^4 ; and

Y is CN, $\text{N}_2\text{H}_2\text{R}^{13}$, $\text{N}_2\text{HR}^{13}\text{R}^{14}$, N_3 , SCN, $\text{SCN}_2\text{H}_2(\text{R}^{15})_2$, $\text{SC}(\text{O})\text{N}(\text{R}^{15})_2$, $\text{SC}(\text{O})\text{NHR}^{15}$, SO_3M , SR^4 , SO_2M , PO_3HM , PO_3M_2 , $\text{P}(\text{O})(\text{OR}^{15})(\text{OR}^{16})$, $\text{P}(\text{O})(\text{OR}^{16})(\text{OM})$, $\text{P}(\text{O})(\text{R}^{15})(\text{OR}^8)$, $\text{P}(\text{O})(\text{OM})\text{R}^{15}$, CO_2M , CO_2H , CO_2R^{11} , $\text{C}(\text{O})\text{R}^{12}$, $\text{C}(\text{O})(\text{SR}^{13})$, SR^5 , SSR^5 , or does not exist.

10

31. The method of claim 28, wherein:

R^5 , R^6 , R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} are the same or different alkyls containing 1-12 carbon atoms; or C_1 or C_2 connections to R^1 or R^3 in cyclic derivatives;

X is CH_2 , O, NH, NMe, S, SO_3M , SH, SR^7 , SO_2M , $\text{S}(\text{O})\text{R}^8$, $\text{S}(\text{O})_2\text{R}^9$, $\text{S}(\text{O})\text{OR}^8$, $\text{S}(\text{O})_2\text{OR}^9$, PO_3M_2 , $\text{P}(\text{O})(\text{OR}^{15})(\text{OR}^{16})$, $\text{P}(\text{O})(\text{OR}^{16})(\text{OM})$, $\text{P}(\text{O})(\text{R}^{15})(\text{OR}^8)$, PO_3HM or $\text{P}(\text{O})(\text{OM})\text{R}^{15}$; and

Y is SO_2M , SO_3M , PO_3HM , PO_3M_2 , $\text{P}(\text{O})(\text{OR}^{15})(\text{OR}^{16})$, $\text{P}(\text{O})(\text{OR}^{16})(\text{OM})$, SR^5 , SR^4 or SSR^5 , or does not exist.

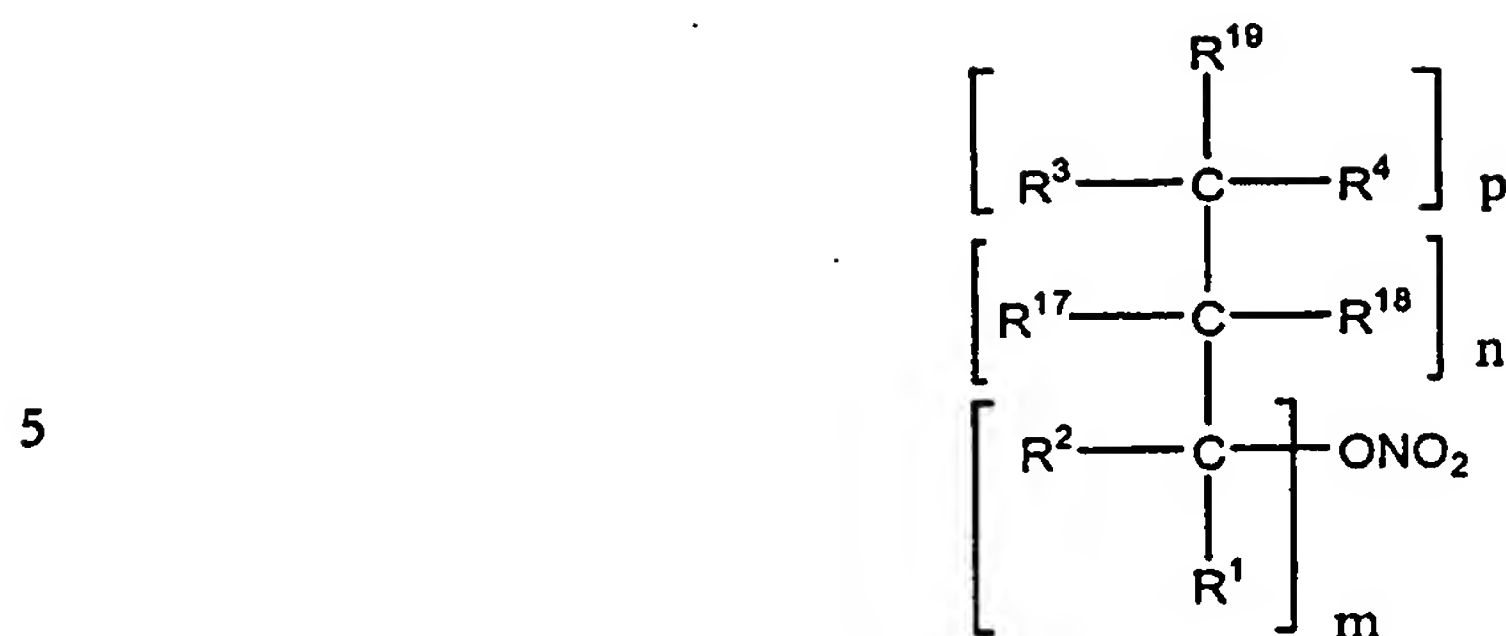
20 32. The method of claim 26, wherein the therapeutic compound is administered orally, intravenously, buccally, transdermally or subcutaneously.

33. The method of claim 26, further comprising administering the therapeutic compound in a pharmaceutically acceptable vehicle.

25

34. A method for effecting cognition enhancement in a subject comprising administering to said subject an effective amount of a organic nitrate, or therapeutically acceptable salt thereof, having the formula (Formula II):

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in which: m, n, p are integers from 0 to 10;

$R^{3,17}$ are each independently hydrogen, a nitrate group, or A;

10 $R^{1,4}$ are each independently hydrogen, or A;

where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted
 15 cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR^6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R^1 and R^3 and/or between R^{17} and R^4 , which optionally contains O, S, NR^6 and unsaturations in the linkage, and optionally bearing
 20 from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. $C=O$, $C=S$, $C=NOH$), which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or
 25 unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R^2, R^5, R^{18}, R^{19} are optionally hydrogen, A, or X-Y;

where X is F, Br, Cl, NO_2 , CH_2 , CF_2 , O, NH, NMe, CN, $NHOH$, N_2H_3 ,
 30 $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3 , S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$,
 $SC(O)NHR^{15}$, SO_3M ,

SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃HM, PO₃M₂,
P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H,
CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³), PO₂H, PO₂M, P(O)(OR¹⁴), P(O)(R¹³), SO, SO₂,
C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵;

5 Y is F, Br, Cl, CH₃, CF₂H, CF₃, OH, NH₂, NHR⁶, NR⁶R⁷, CN, NHOH, N₂H₃,
N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂,
SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM,
PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M,
CO₂H, CO₂R¹¹, C(O)R¹², C(O)(OR¹³), C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵, or does not exist;

10 R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ are the same or different alkyl or acyl
groups containing 1-24 carbon atoms which may contain 1-4 ONO₂ substituents; or C₁ -
C₆ connections to R¹ - R⁴ in cyclic derivatives; or are each independently hydrogen, a
nitrate group, or W; and

M is H, Na⁺, K⁺, NH₄⁺, N⁺H_kR¹¹_(+k) where k is 0-3, or other pharmaceutically
15 acceptable counterion;
and with the proviso,

when m = n = p = 1; R¹⁹, R², R¹⁸, R¹ = H; R¹⁷, R³ are nitrate groups;
that R⁴ is not H or C₁ - C₃ alkyl.

20 35. The method of claim 34, wherein:

R¹⁹ is X-Y.

36. The method of claim 35, wherein:

25 R¹ and R³ are the same or different and selected from H, C₁-C₄ alkyl chains which
may include one O, linking R¹ and R³ to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl
rings, which rings optionally bear hydroxyl substituents;

R² and R⁴, are the same or different and selected from H, a nitrate group, C₁-C₄
alkyl optionally bearing 1-3 nitrate group, and acyl groups (-C(O)R⁵);

R⁷, R¹¹ are the same or different C₁ - C₈, alkyl or acyl;

$R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$ are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 or C_2 connections to $R^1 - R^3$ in cyclic derivatives; and

M is H, Na^+ , K^+ , NH_4^+ , $N^+H_kR^{11}_{(4-k)}$ where k is 0-3.

5

37. The method of claim 36, wherein:

$m = 1, n = 0, p = 1;$

X is $CH_2, O, NH, NMe, CN, NHOH, N_2H_3, N_2H_2R^{13}, N_2HR^{13}R^{14}, N_3, S, SCN, SCN_2H_2(R^{15})_2, SCN_2H_3(R^{15}), SC(O)N(R^{15})_2, SC(O)NHR^{15}, SO_3M, SH, SR^7, SO_2M, S(O)R^8, S(O)_2R^9, S(O)OR^8, S(O)_2OR^9, PO_3HM, PO_3M_2, P(O)(OR^{15})(OR^{16}), P(O)(OR^{16})(OM), P(O)(R^{15})(OR^8), P(O)(OM)R^{15}, CO_2M, CO_2H, CO_2R^{11}, C(O), C(O)R^{12}, C(O)(OR^{13}), PO_2M, P(O)(OR^{14}), P(O)(R^{13}), SO, SO_2, C(O)(SR^{13}), SSR^4;$ and

Y is $CN, N_2H_2R^{13}, N_2HR^{13}R^{14}, N_3, SCN, SCN_2H_2(R^{15})_2, SC(O)N(R^{15})_2, SC(O)NHR^{15}, SO_3M, SR^4, SO_2M, PO_3HM, PO_3M_2, P(O)(OR^{15})(OR^{16}), P(O)(OR^{16})(OM), P(O)(R^{15})(OR^8), P(O)(OM)R^{15}, CO_2M, CO_2H, CO_2R^{11}, C(O)R^{12}, C(O)(SR^{13}), SR^5, SSR^5,$ or does not exist.

38. The method of claim 36, wherein:

$m = 1, n = 0, p = 1;$

$R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$ are the same or different alkyls containing 1-12 carbon atoms; or C_1 or C_2 connections to R^1 or R^3 in cyclic derivatives;

X is $CH_2, O, NH, NMe, S, SO_3M, SH, SR^7, SO_2M, S(O)R^8, S(O)_2R^9, S(O)OR^8, S(O)_2OR^9, PO_3M_2, P(O)(OR^{15})(OR^{16}), P(O)(OR^{16})(OM), P(O)(R^{15})(OR^8), PO_3HM$ or $P(O)(OM)R^{15};$ and

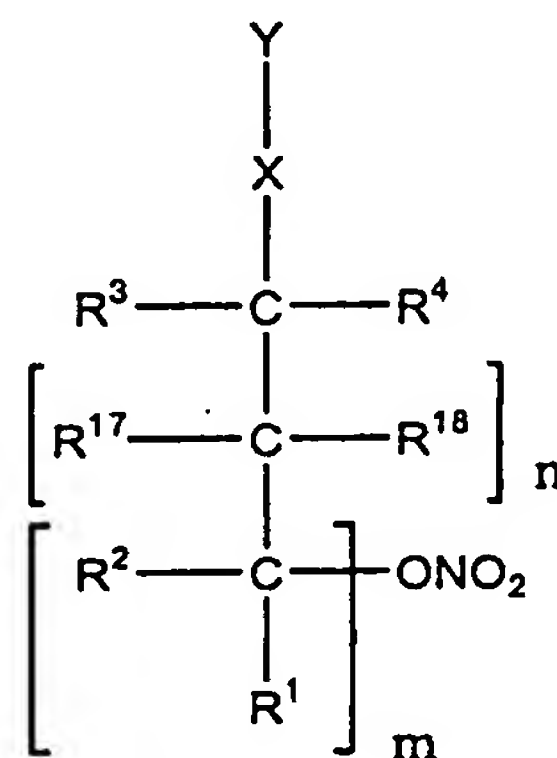
Y is $SO_2M, SO_3M, PO_3HM, PO_3M_2, P(O)(OR^{15})(OR^{16}), P(O)(OR^{16})(OM), SR^5, SR^4$ or $SSR^5,$ or does not exist.

39. A method for mitigating neurodegeneration in a subject, comprising administering to said subject an effective amount of a therapeutic compound such that mitigation of neurodegeneration occurs, wherein guanylyl cyclase is activated and cGMP level is increased.

40. The method of claim 34, wherein the therapeutic compound is administered orally, intravenously, buccally, transdermally or subcutaneously.

41. The method of claim 34, further comprising administering the therapeutic compound
5 in a pharmaceutically acceptable vehicle.

42. Organic nitrates containing at least one nitrate group having the general formula (Formula III):



10 in which: m is an integer from 1 to 10; n is an integer from 0 to 10;

$\text{R}^{3,4,17}$ are each independently hydrogen, a nitrate group, or A;

where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR^6 and unsaturations in the chain, optionally
15 bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR^6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons,
20 between R^1 and R^3 and/or between R^{17} and R^4 , which optionally contains O, S, NR^6 and unsaturations in the linkage,

and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

10 R², R⁵, R¹⁸, are optionally hydrogen, A, or X-Y;

where X is F, Br, Cl, NO₂, CH₂, CF₂, O, NH, NMe, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵,
15 CO₂M, CO₂H, CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³), PO₂H, PO₂M, P(O)(OR¹⁴), P(O)(R¹³), SO, SO₂, C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵;

Y is F, Br, Cl, CH₃, CF₂H, CF₃, OH, NH₂, NHR⁶, NR⁶R⁷, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M,
20 CO₂H, CO₂R¹¹, C(O)R¹², C(O)(OR¹³), C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵, or does not exist;

R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO₂ substituents; or C₁ - C₆ connections to R¹ - R⁴ in cyclic derivatives; or are each independently hydrogen, a
25 nitrate group, or W; and

M is H, Na⁺, K⁺, NH₄⁺, N⁺H_kR¹¹_(4-k) where k is 0-3, or other pharmaceutically acceptable counterion;

and with the proviso that,

when m=0; n=1;

R^{18} and R^3 are the same or different and selected from H, a nitrate group, $C_1 - C_4$ alkyl and chains, which may include one O, linking R^{18} and R^3 to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which rings optionally bear hydroxyl substituents;

R^{17} and R^4 , are the same or different and selected from H, a nitrate group, $C_1 - C_4$ alkyl optionally bearing 1-3 nitrate group, and acyl groups ($-C(O)R^5$);

$R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$ are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 or C_2 connections to R^{18}, R^{17} , or R^3 in cyclic derivatives;

R^7, R^{11} are $C_1 - C_8$ alkyl or acyl;

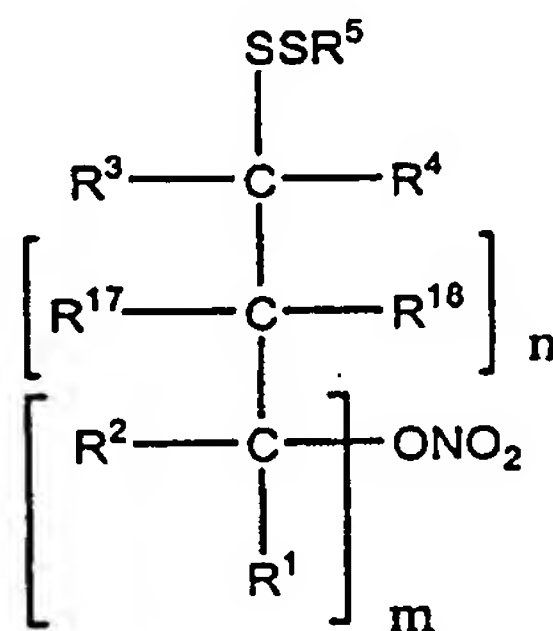
10 M is H, Na^+ , K^+ , NH_4^+ , $N^+H_kR^{11}_{(4-k)}$ where k is 0-3;

X is CH_2 , O, NH, NMe, CN, NHOH, N_2H_3 , $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3 , S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SH, SR^7 , SO_2M , $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3HM , PO_3M_2 , $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M , CO_2H , CO_2R^{11} , $C(O)$, $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2M , $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2 , $C(O)(SR^{13})$, or SSR^4 ;

15 that Y is not CN, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3 , SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SH, SO_2M , PO_3M_2 , PO_3HM , $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(OM)R^{15}$, CO_2M , CO_2H , CO_2R^{11} , $C(O)R^{12}$, $C(O)(SR^{13})$, SR^4 , SR^5 , or SSR^5 , or does not exist.

20

43. A method for preparing a compound represented by the formula (Formula V):



in which $m, n = 0 - 10$;

R^4 is hydrogen, a nitrate group, or A;

R^3, R^{17}, R^{18} are each independently hydrogen or A;

and R^5 is A;

- 5 where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR_6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the
- 10 aliphatic ring, which optionally contains O, S, NR_6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R_1 and R_3 and/or between R_2 and R_4 , which optionally contains O, S, NR_6 and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or
- 15 aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. $C=O$, $C=S$, $C=NOH$), which optionally contains O, S, NR_6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl
- 20 group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;
- the method comprising:

- 25 reacting an appropriate halo-alcohol with a nitrating reagent selected from a mixture of nitric and sulfuric acid in a mixture of water and a selected organic solvent, acetyl nitrate, nitronium tetrafluoroborate, or reacting an appropriate halo-alkene with thallium nitrate in pentanes, under conditions such that an appropriate halo-organic nitrate is formed;

- 30 reacting an appropriate halo-organic nitrate with a thiol sulfonate salt so as to produce a selected Bunte salt;

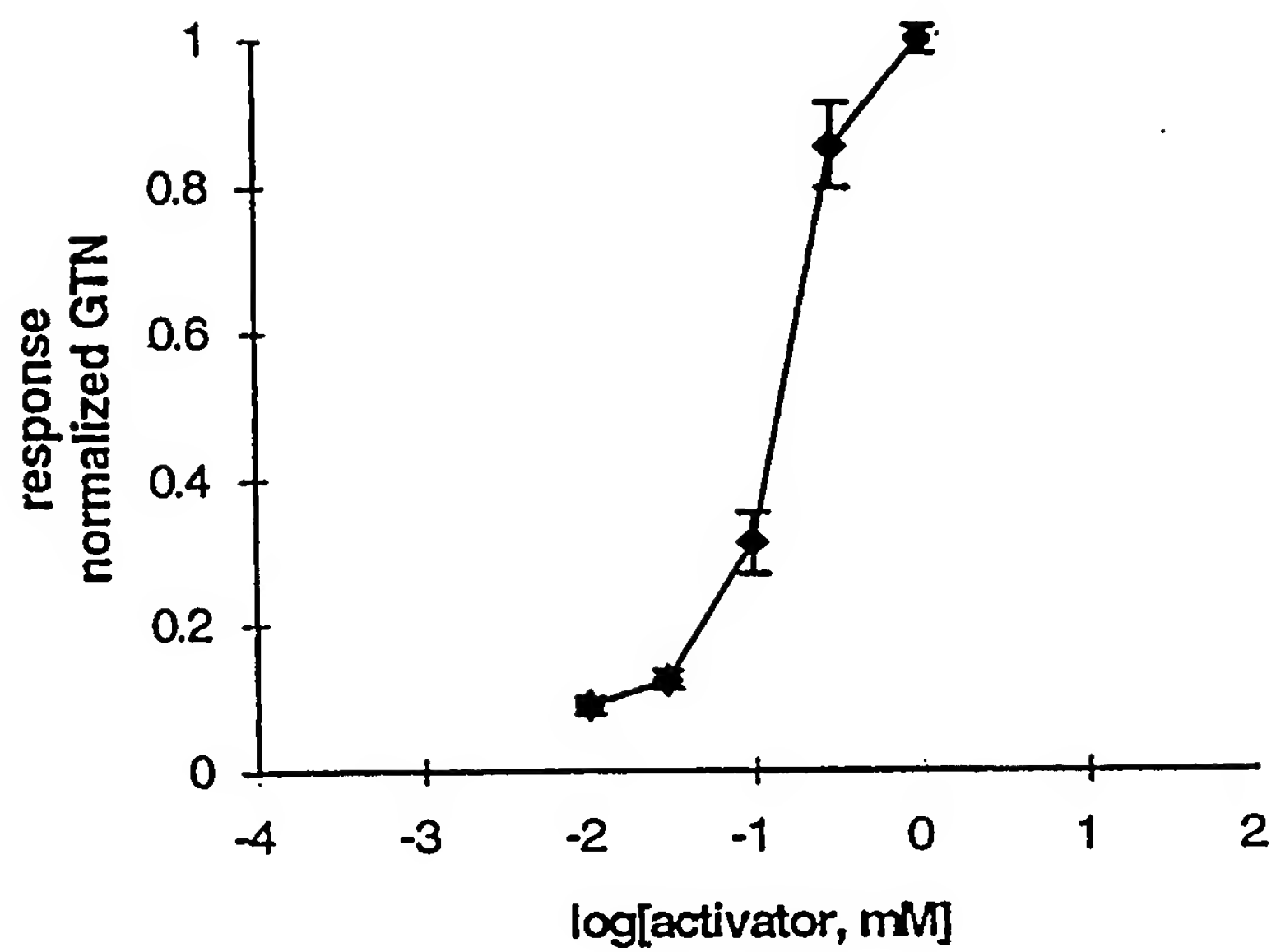
reacting an appropriate Bunte salt, optionally with an oxidizing agent (e.g. 30% hydrogen peroxide) in the presence of an appropriate catalyst (e.g. sulfuric acid), under conditions such that the compound of Formula 5 is prepared;

5 reacting an appropriate disulfide in a thiol/disulfide exchange reaction with an organic thiolate salt, under conditions such that a compound of Formula 5 is formed.

44. The method of claim 2, wherein administering the therapeutic compound to the subject modulates cellular free radical damage.

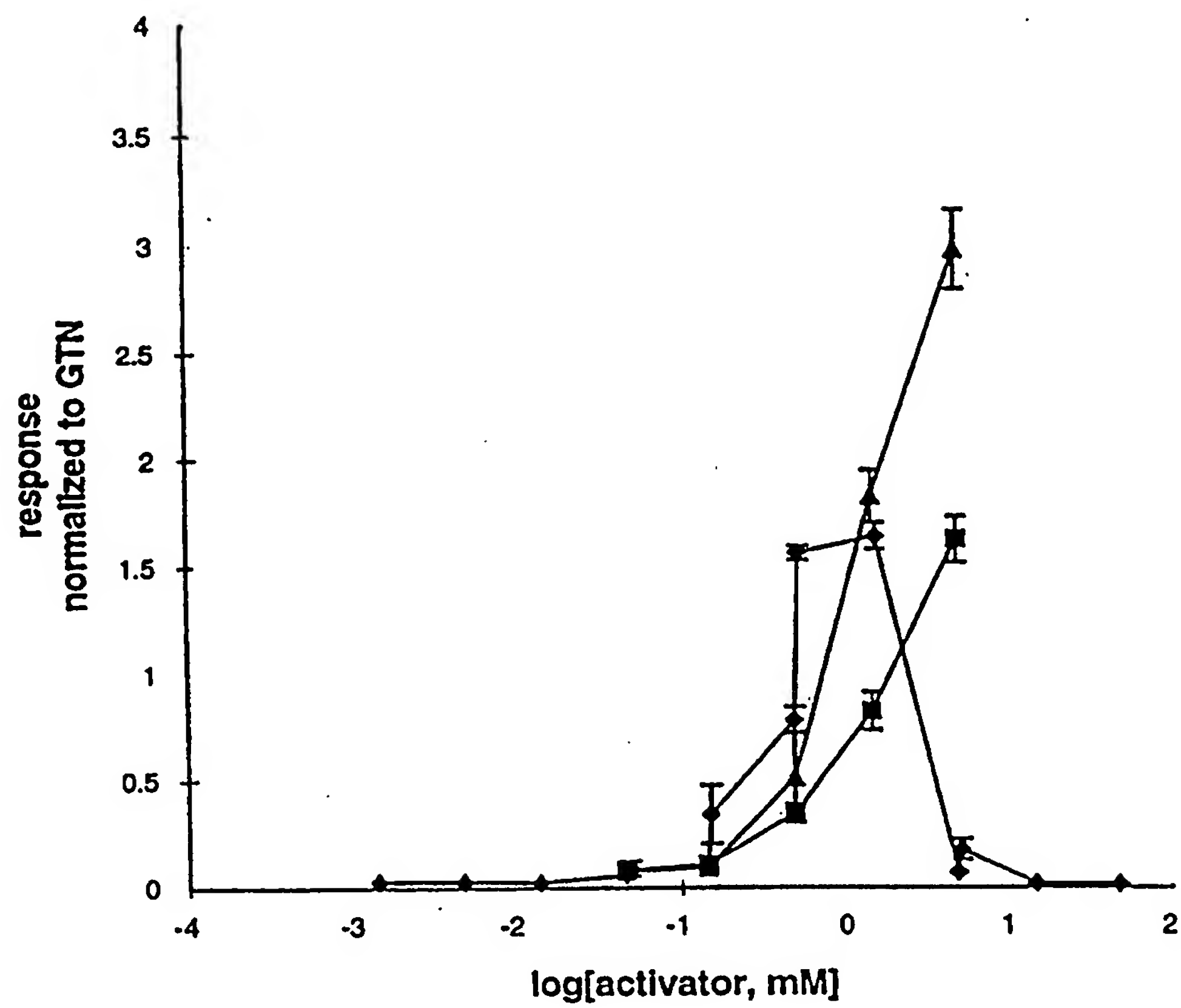
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FIGURE 1



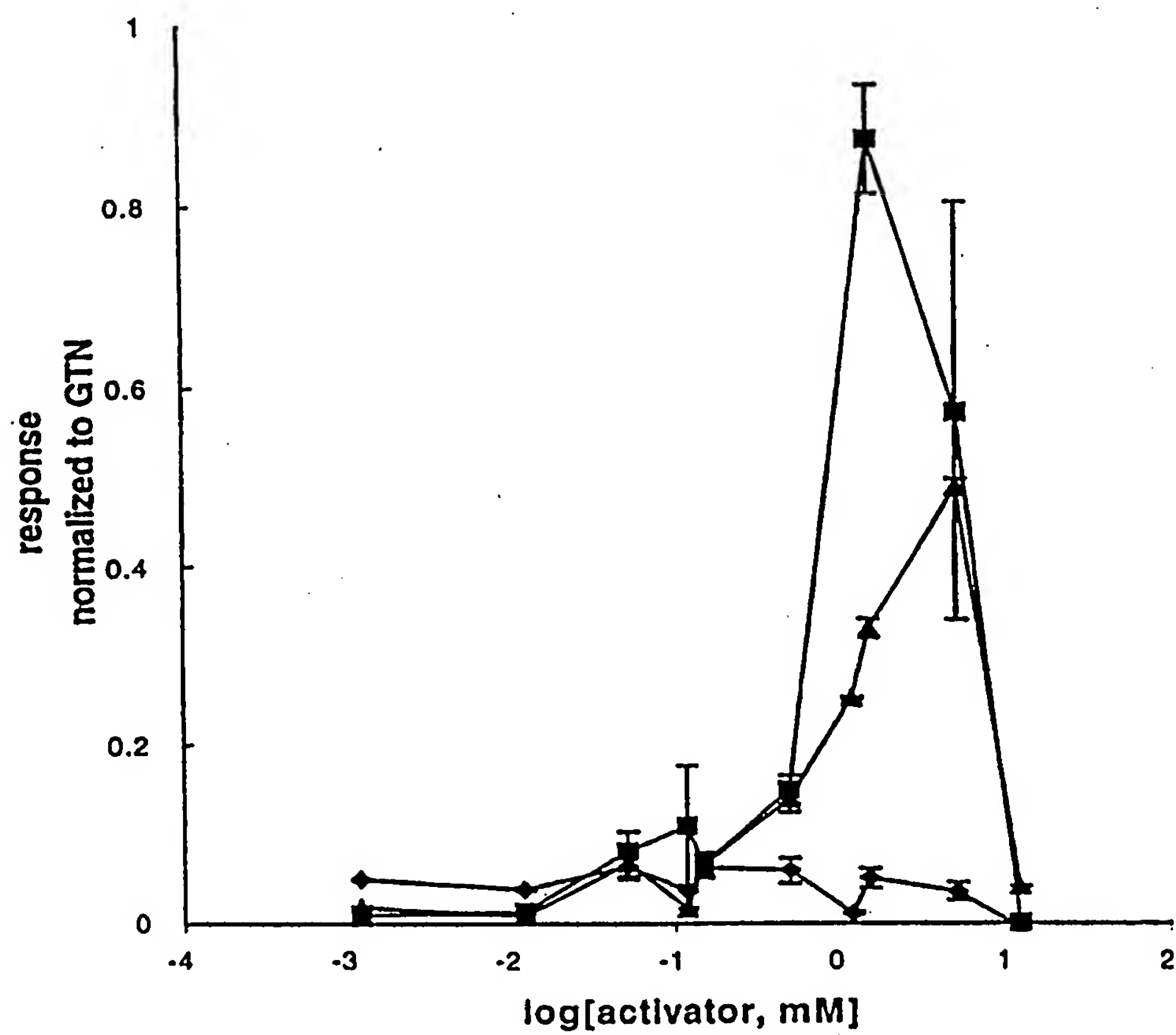
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FIGURE 2



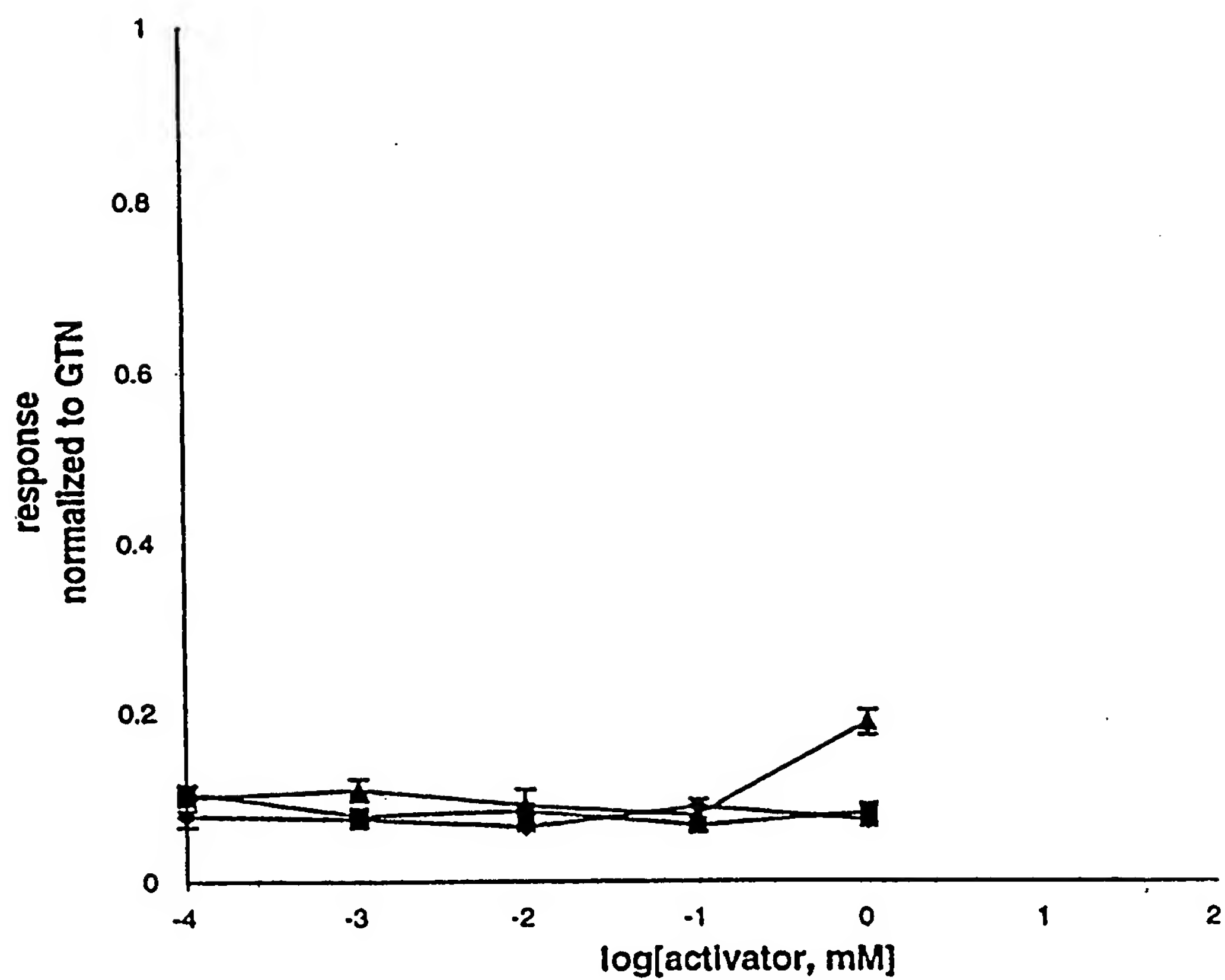
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FIGURE 3



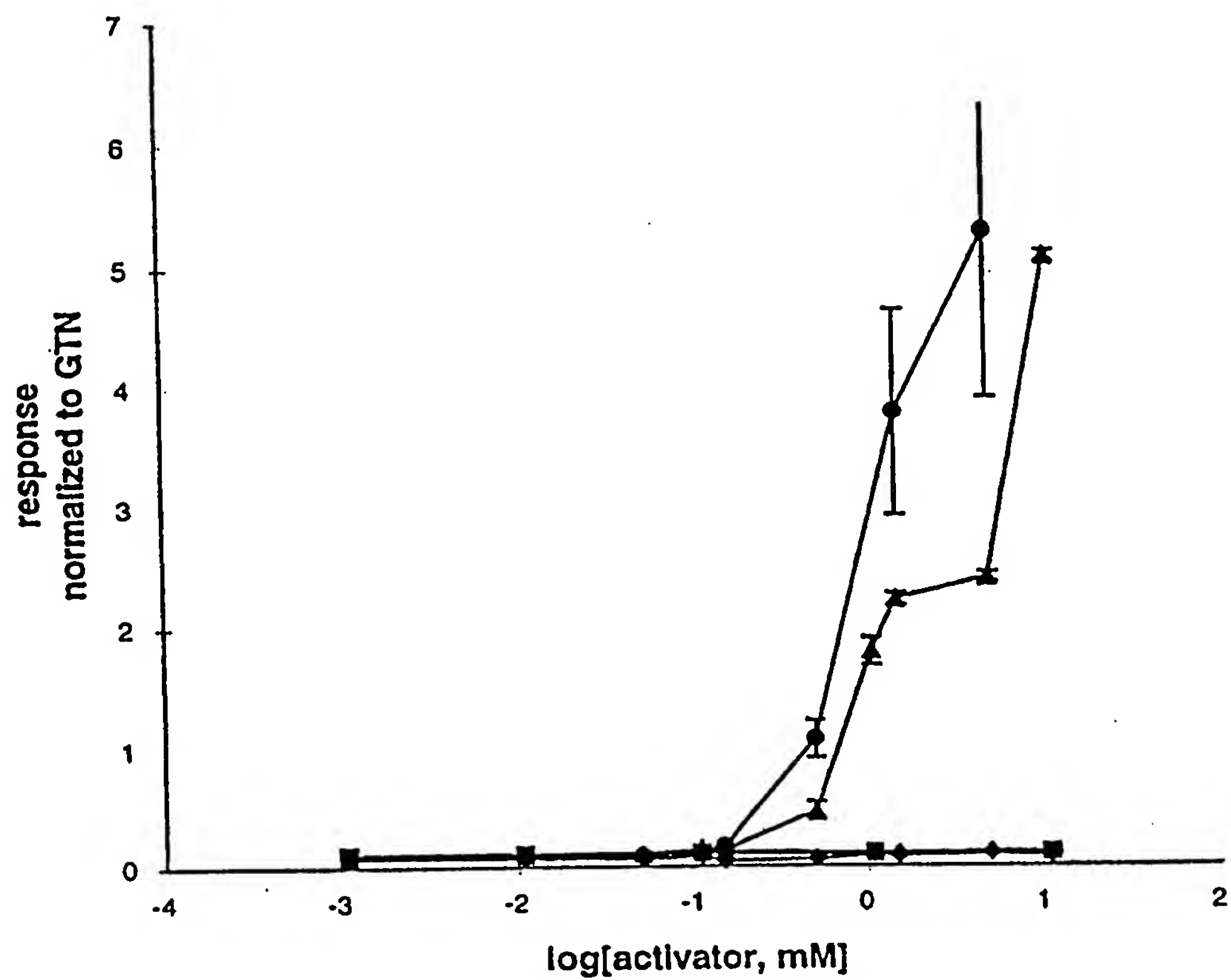
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FIGURE 4



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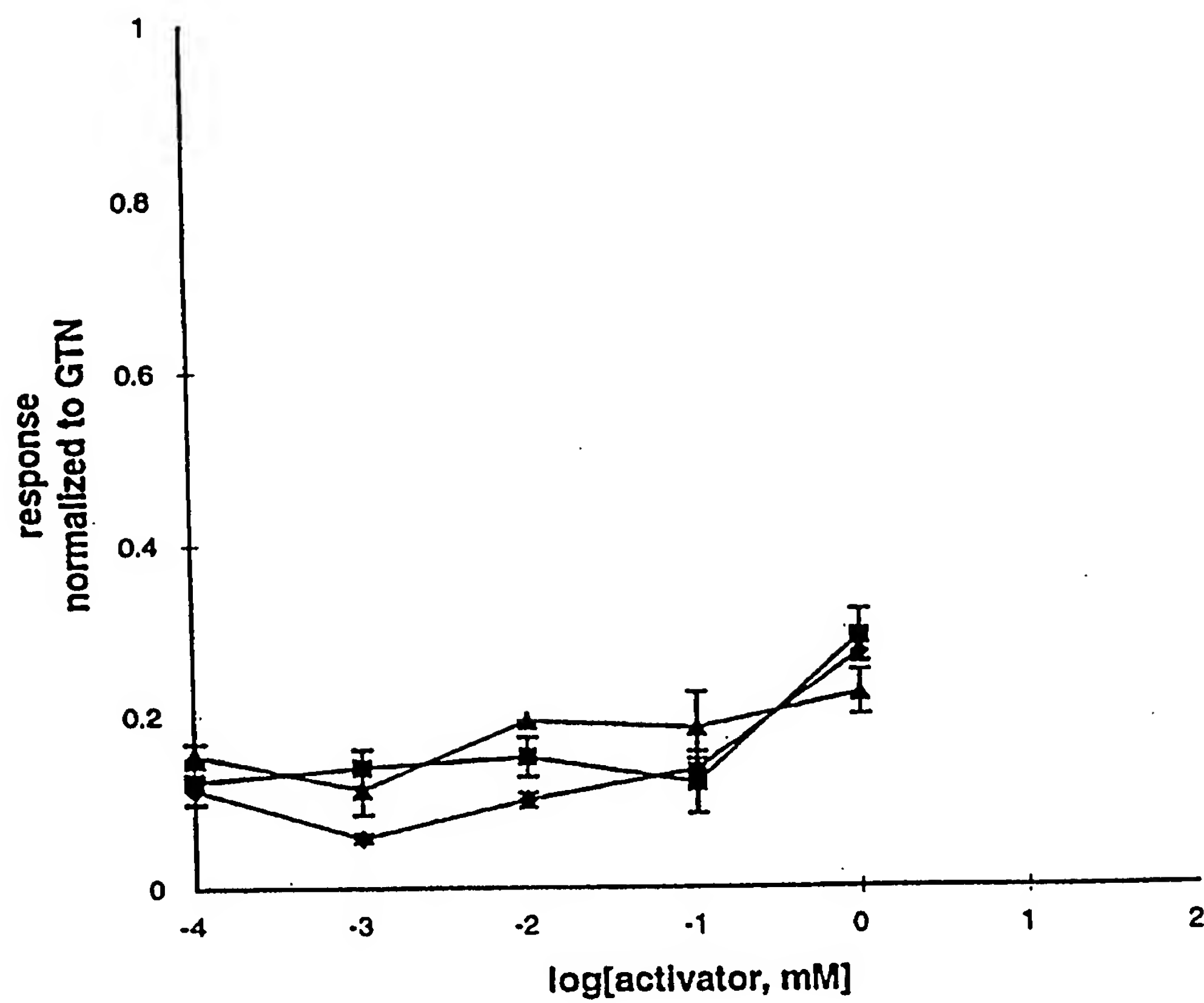
FIGURE 5



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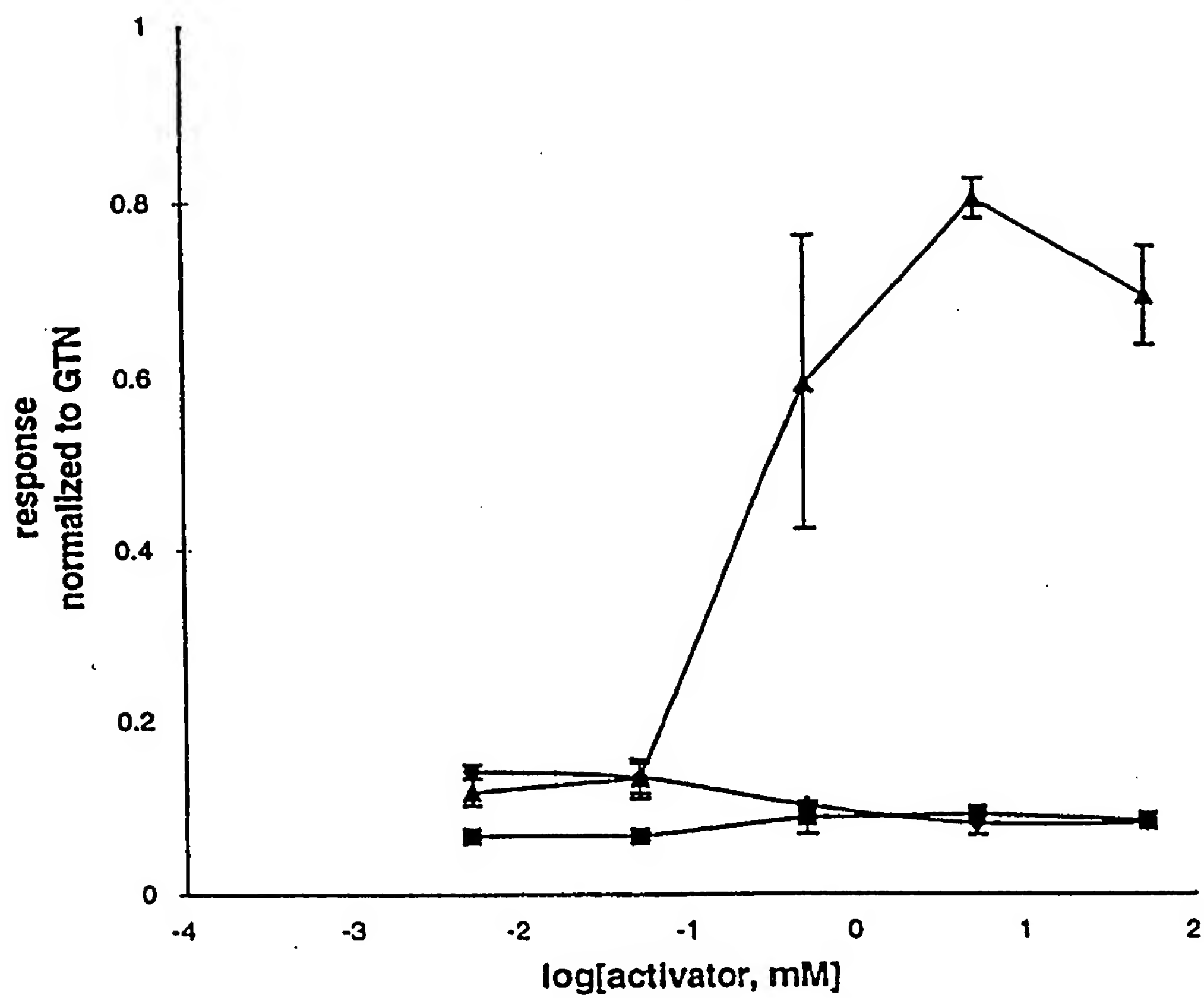
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FIGURE 6



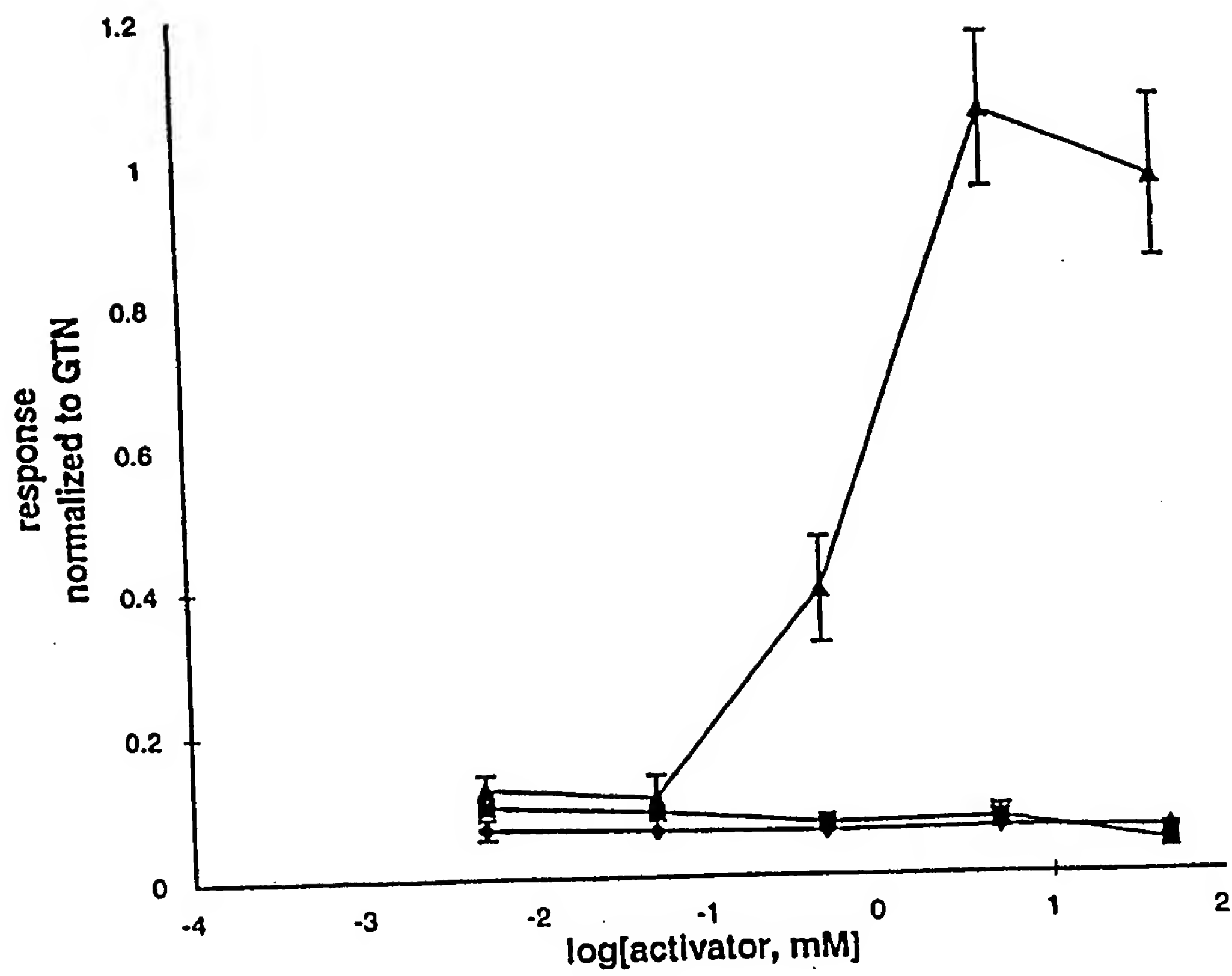
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FIGURE.7



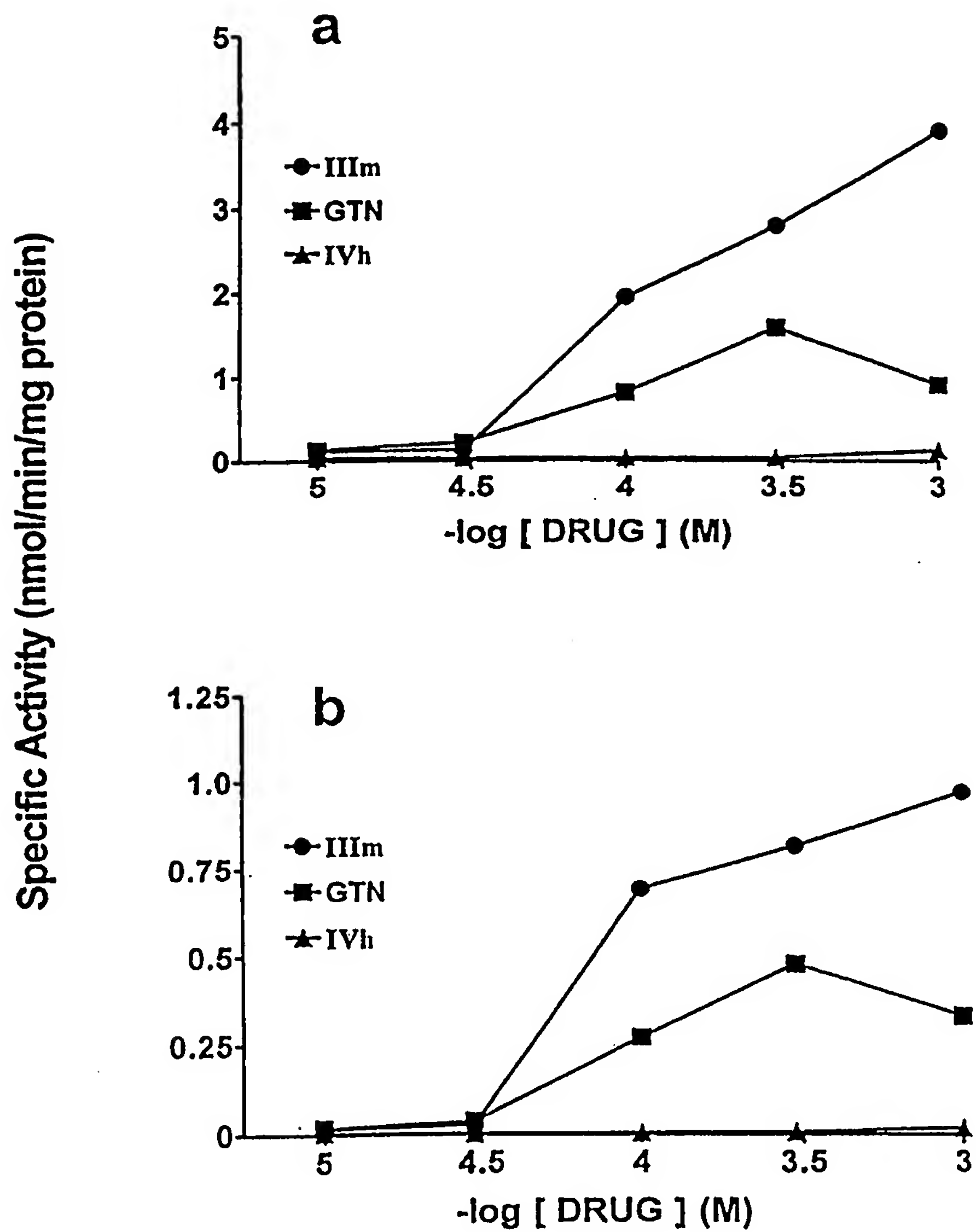
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FIGURE 8



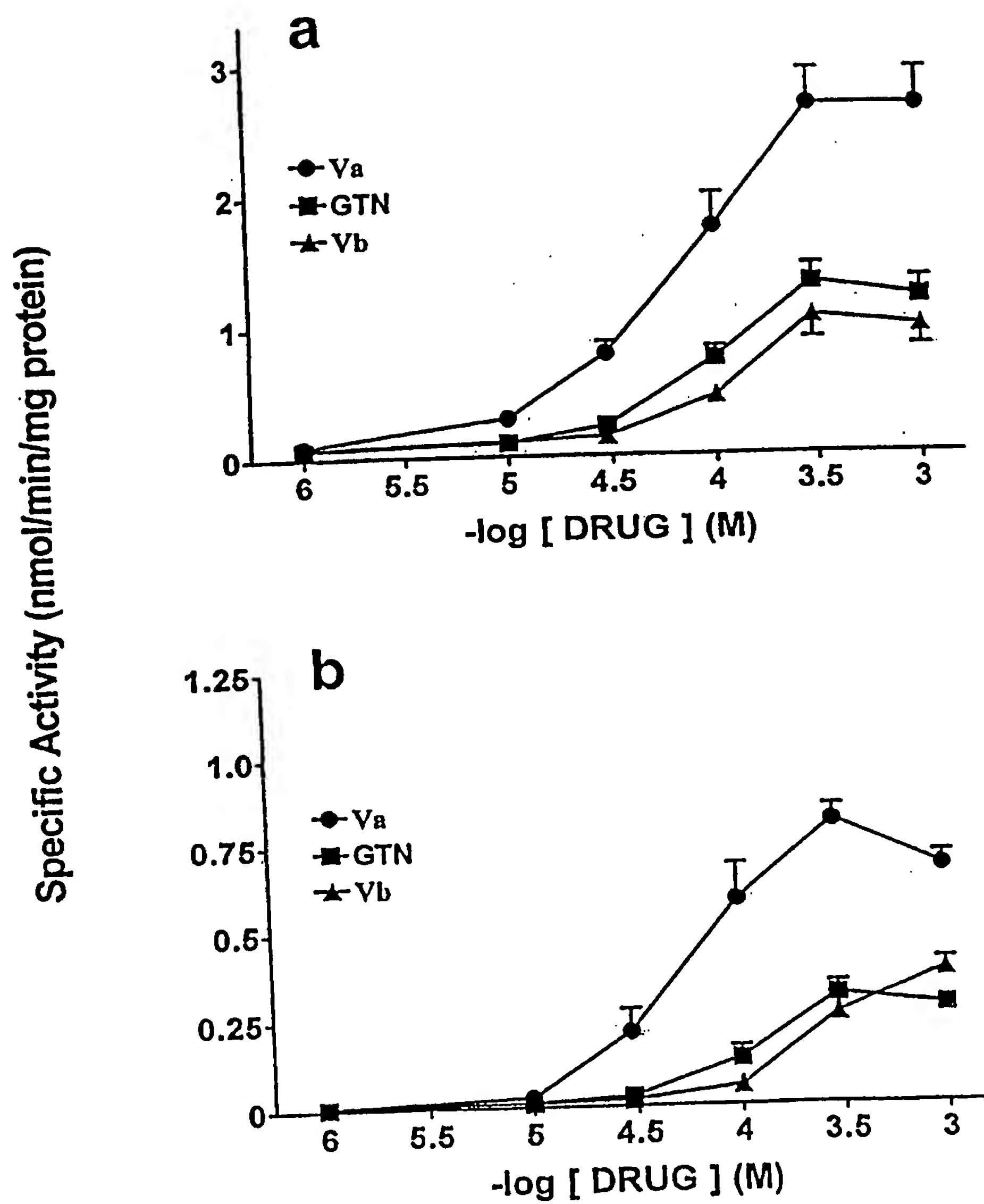
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FIGURE 9



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FIGURE 10



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FIGURE 11

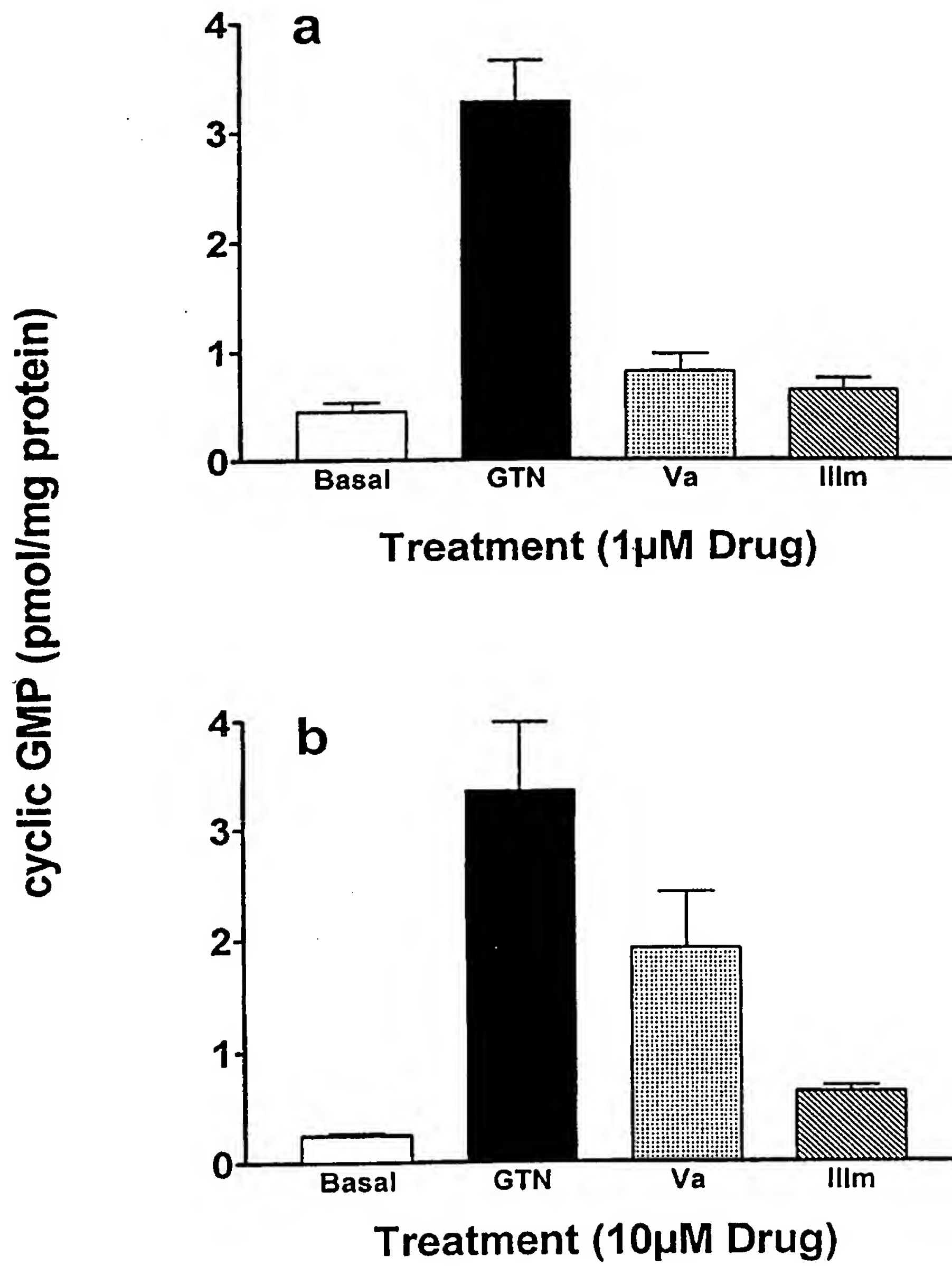
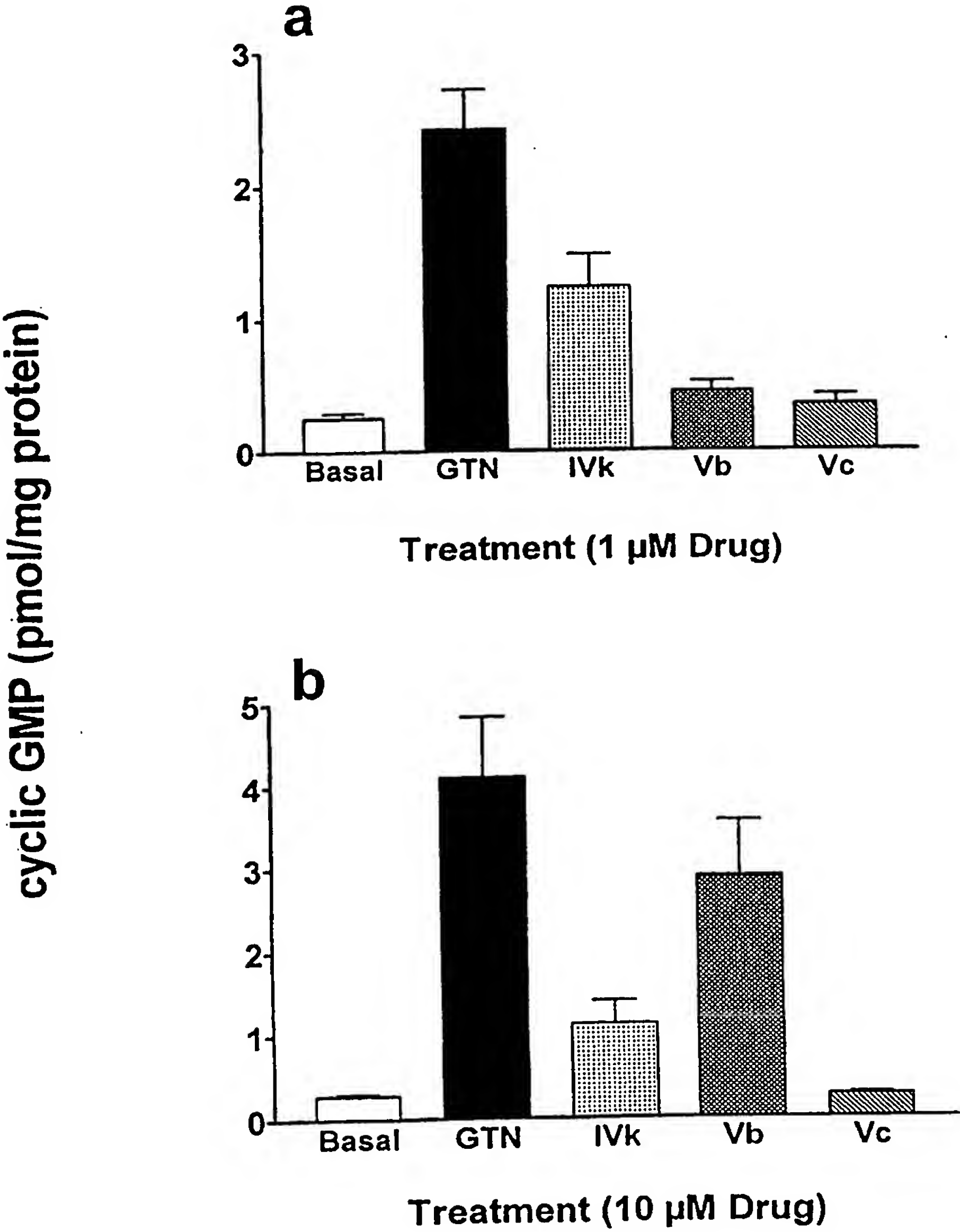
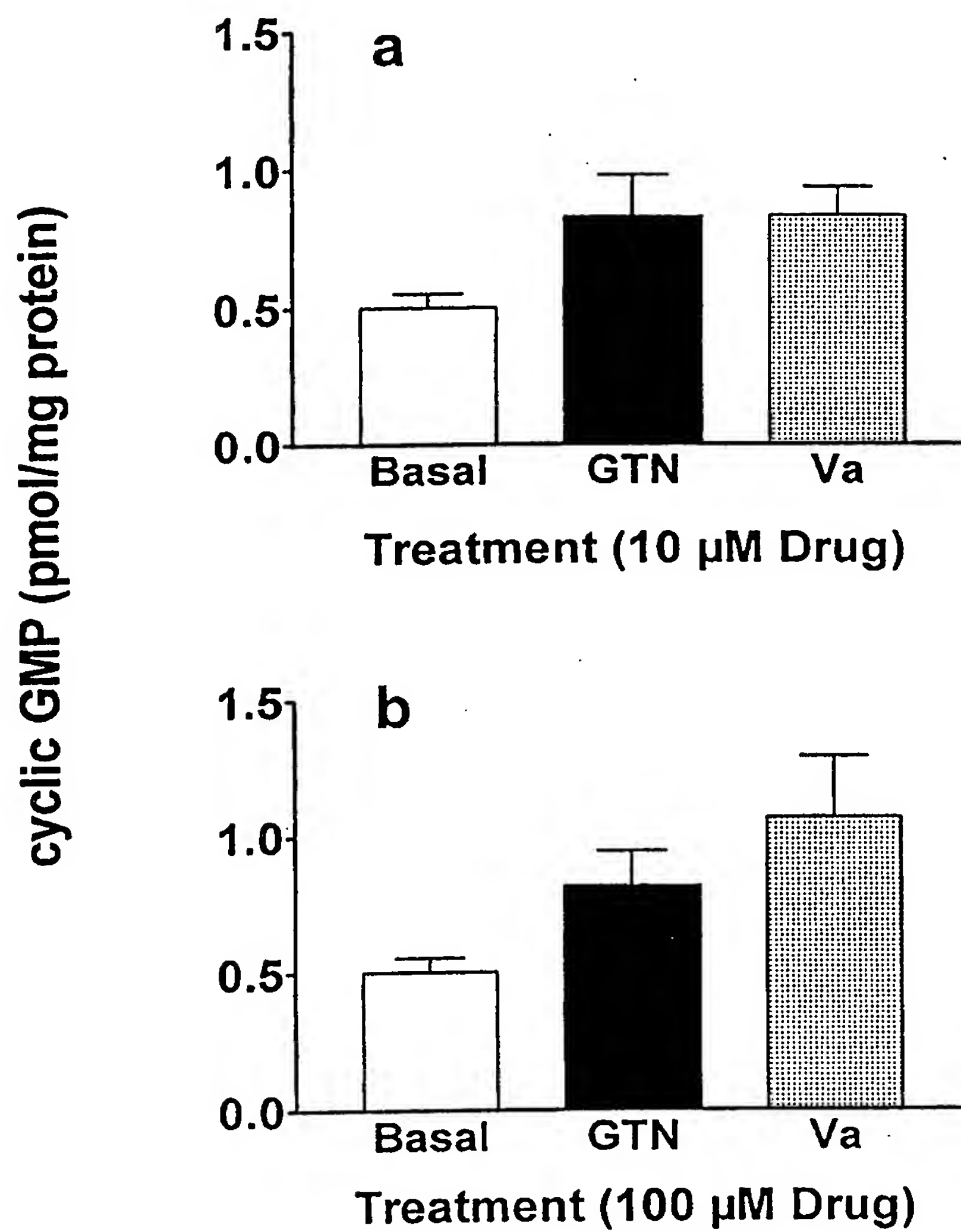


FIGURE 12



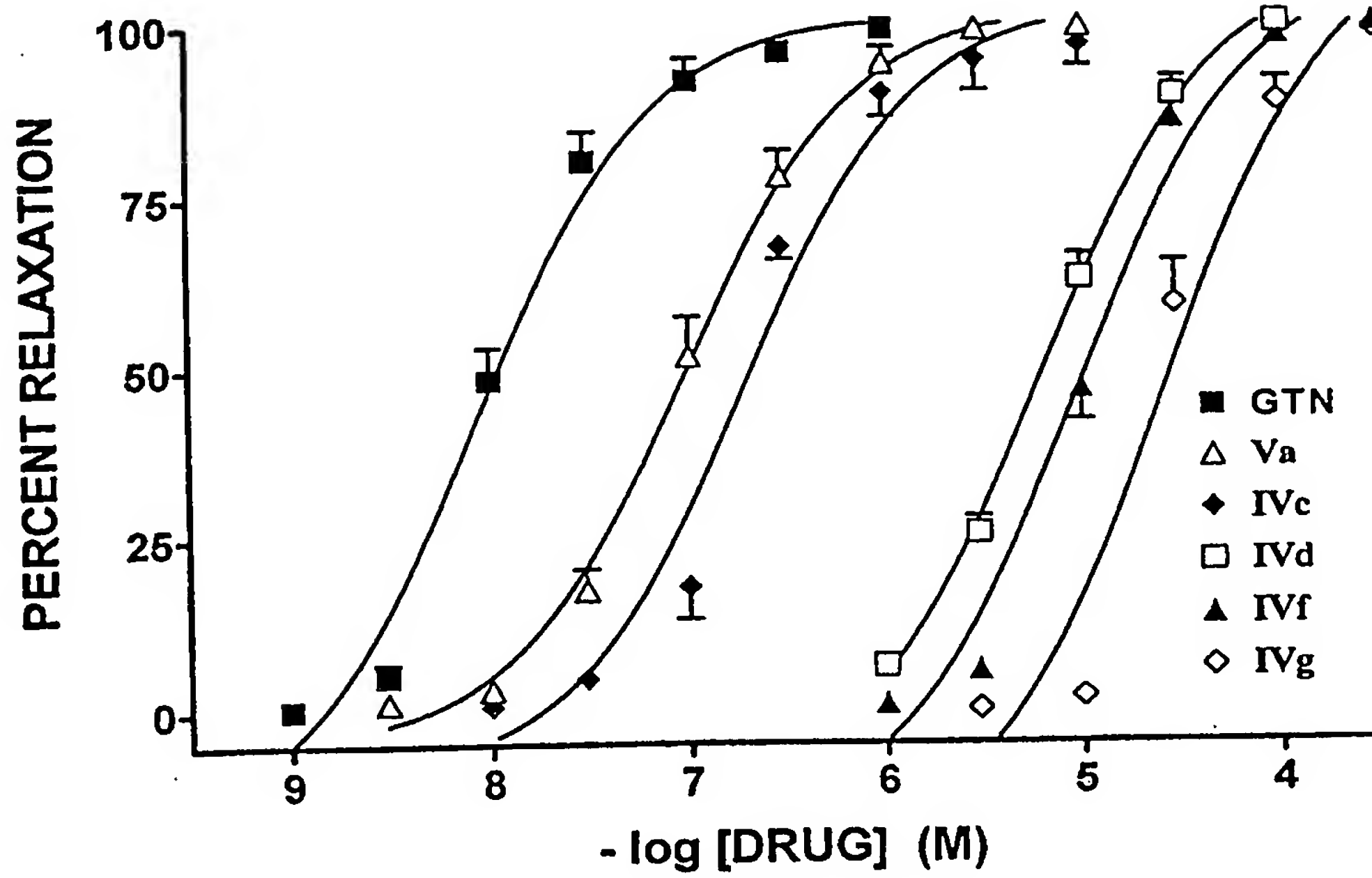
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FIGURE 13



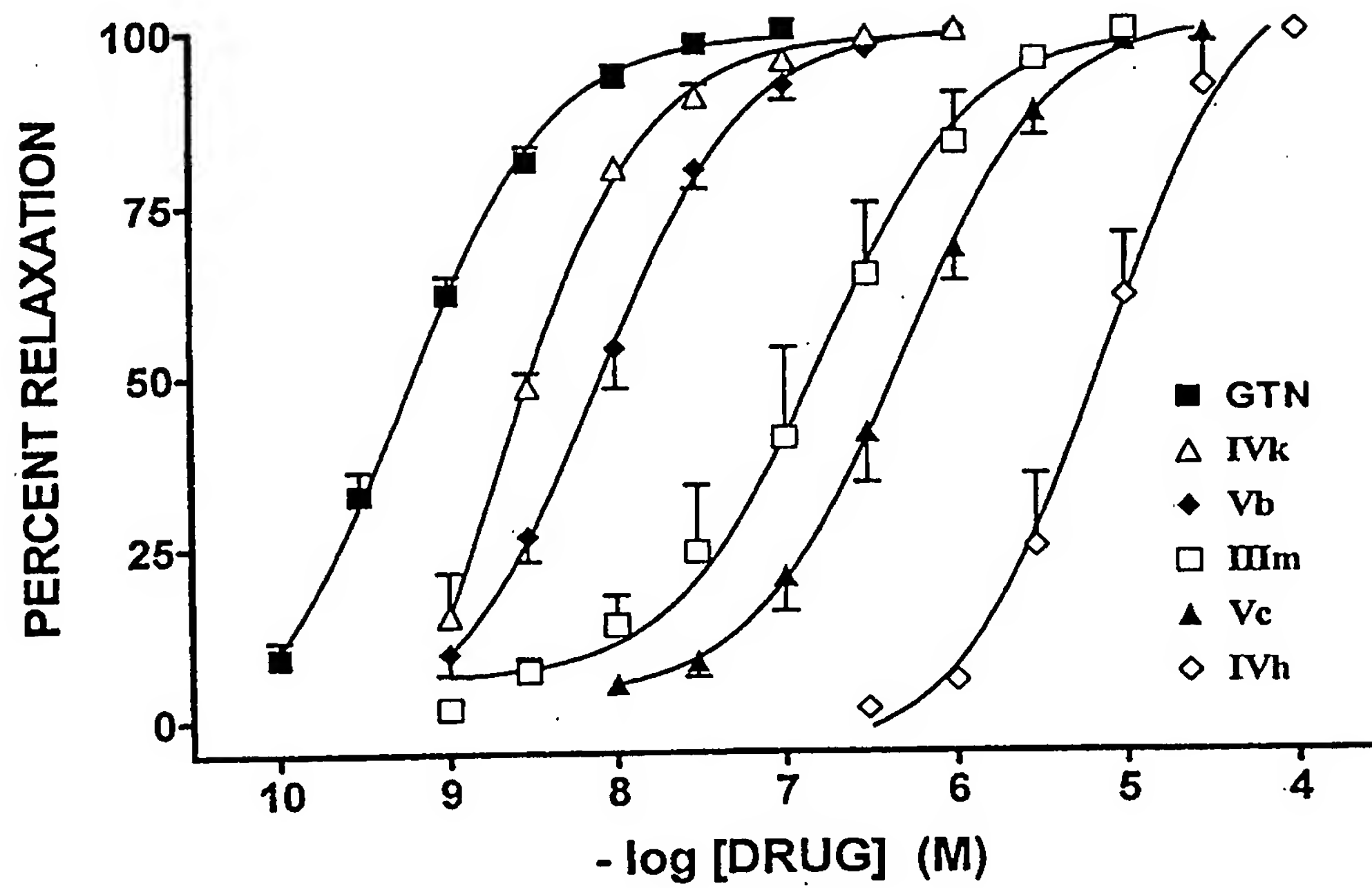
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FIGURE 14



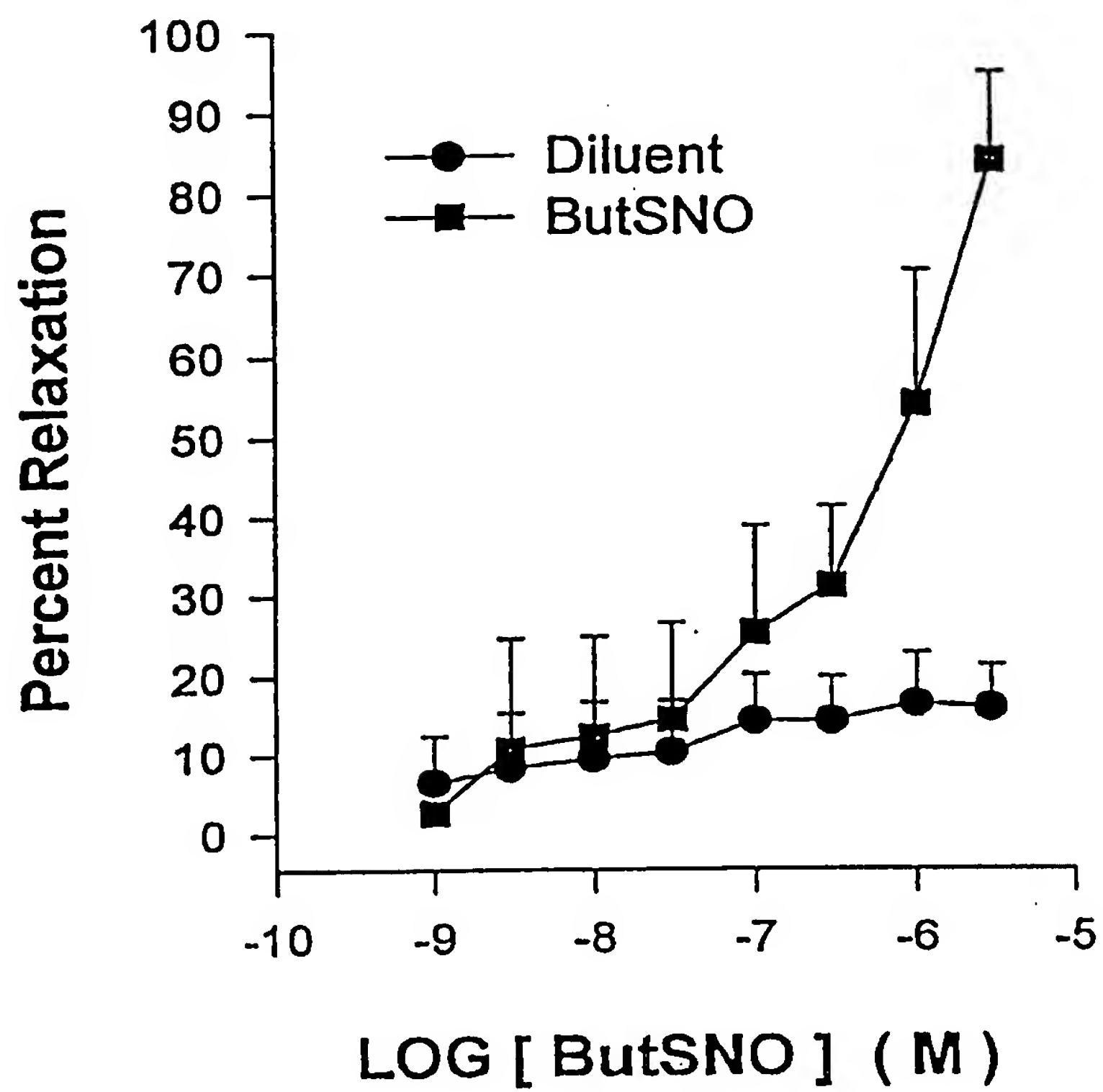
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FIGURE 15



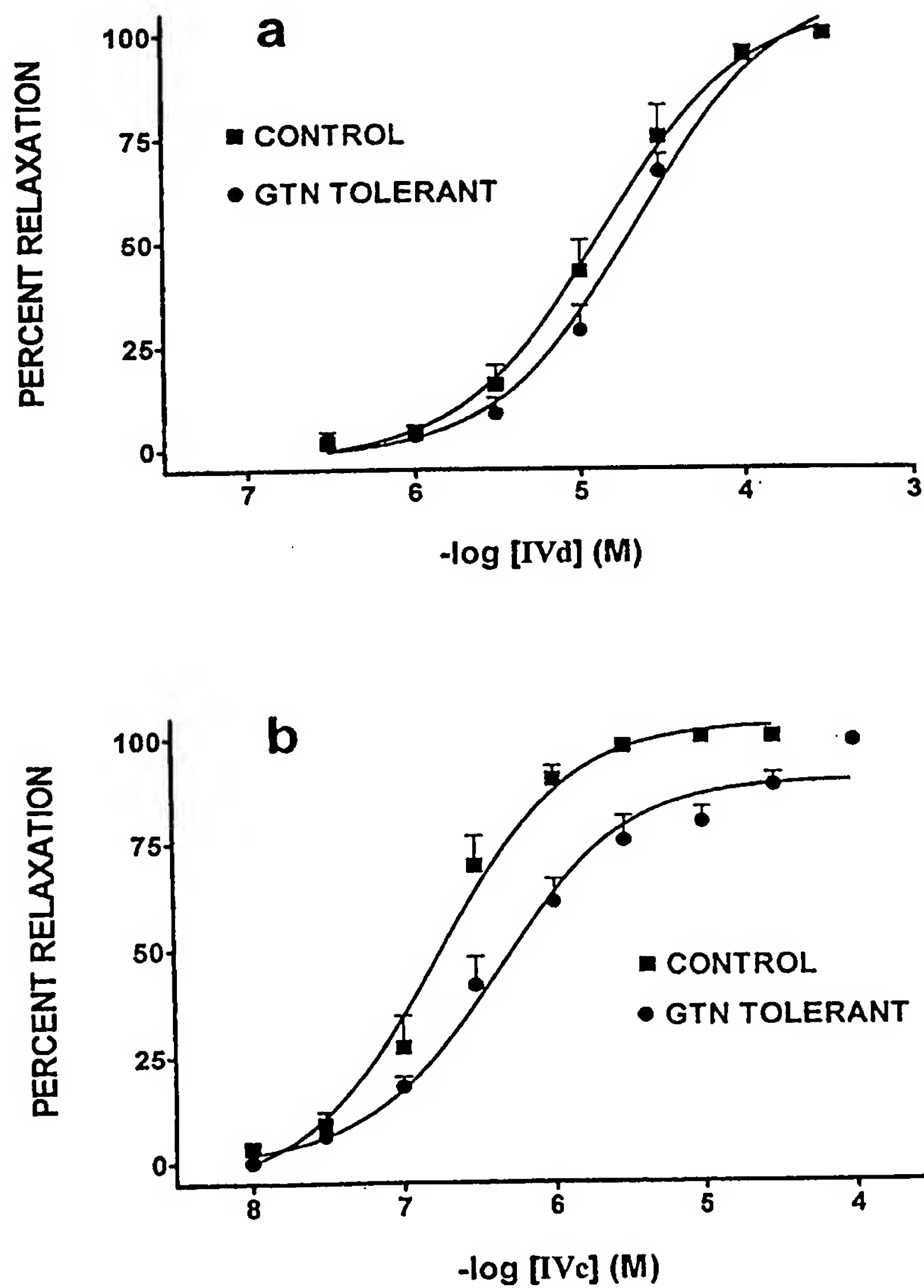
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FIGURE 16



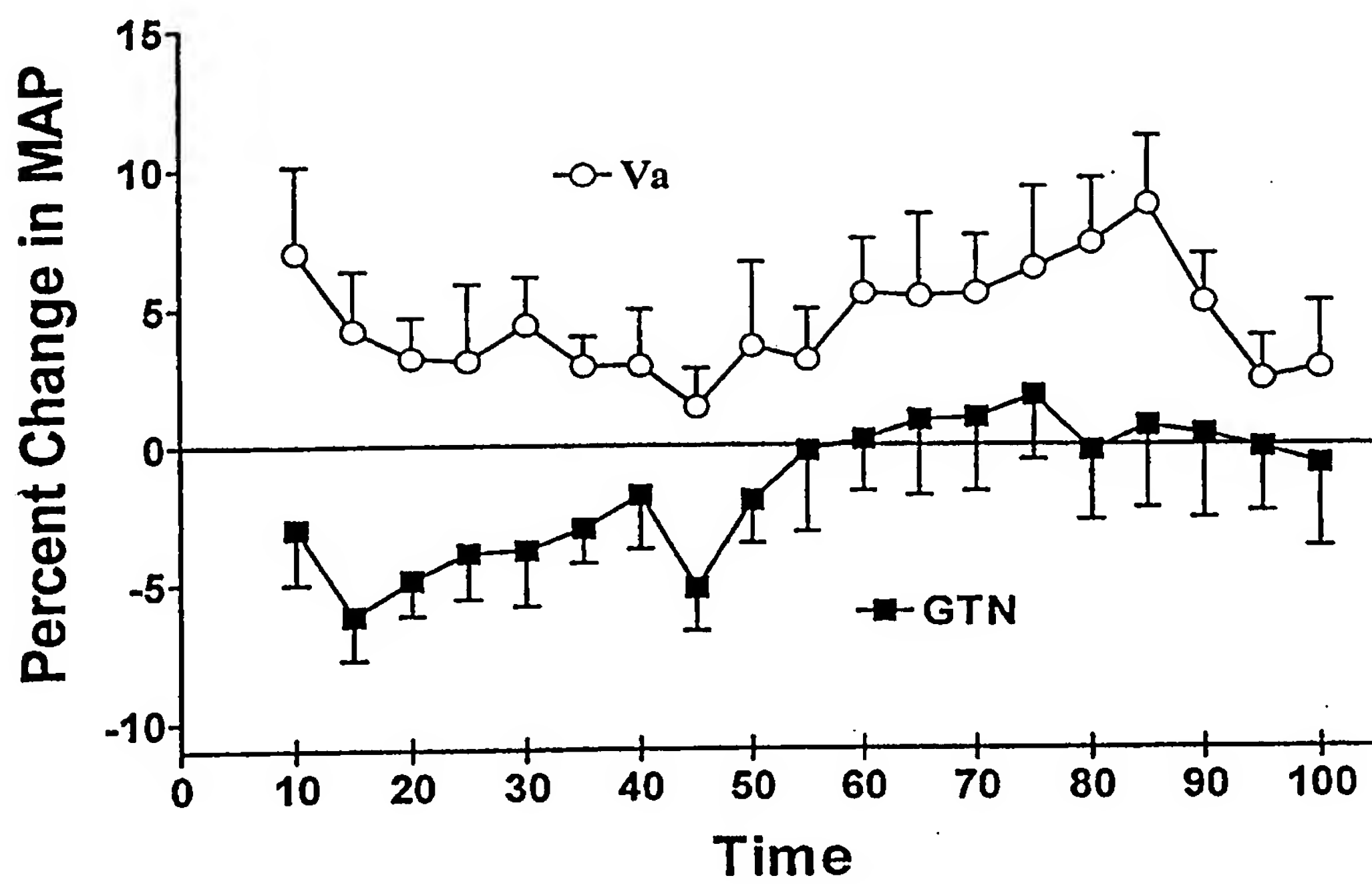
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FIGURE 17



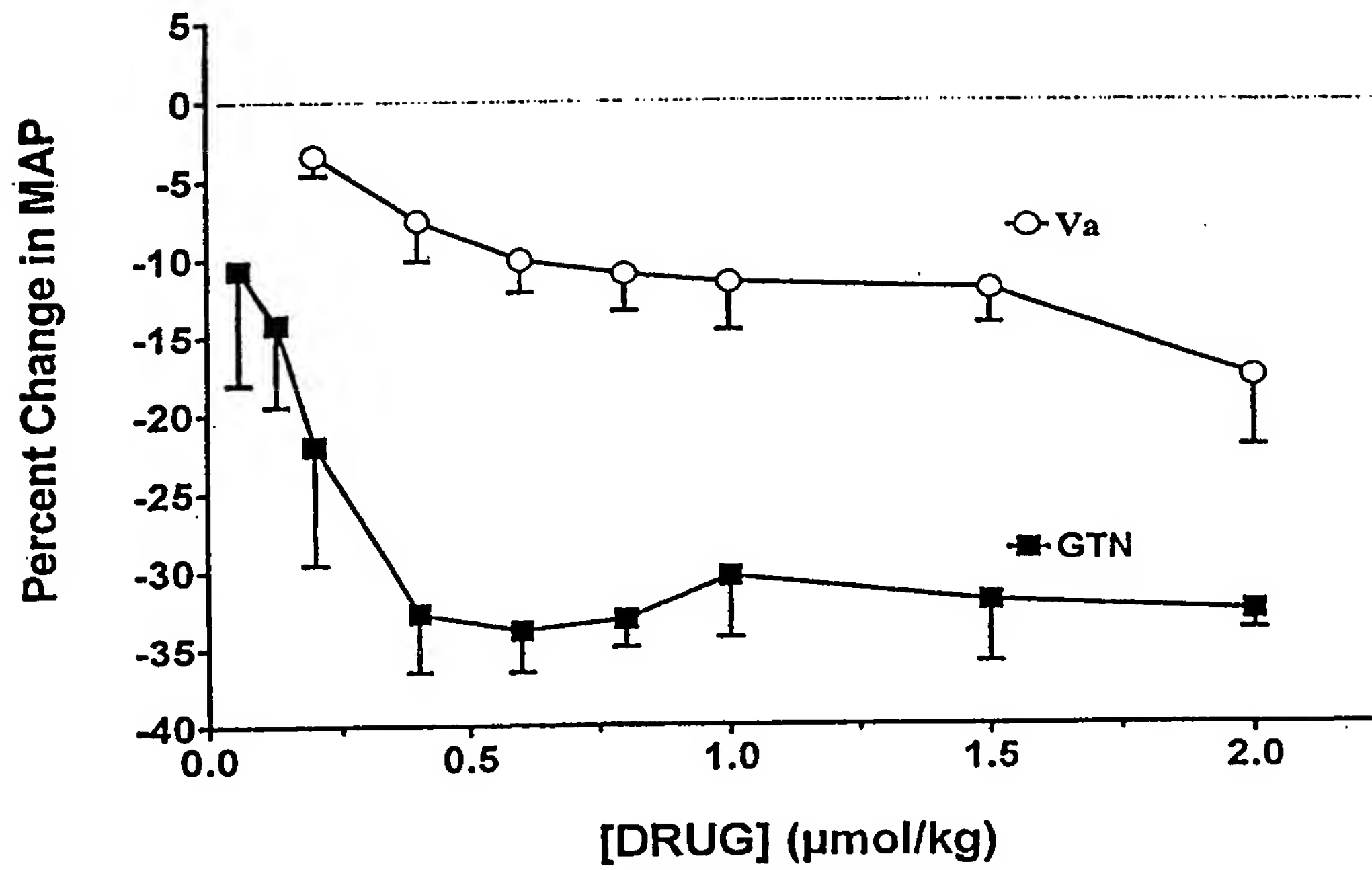
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FIGURE 18



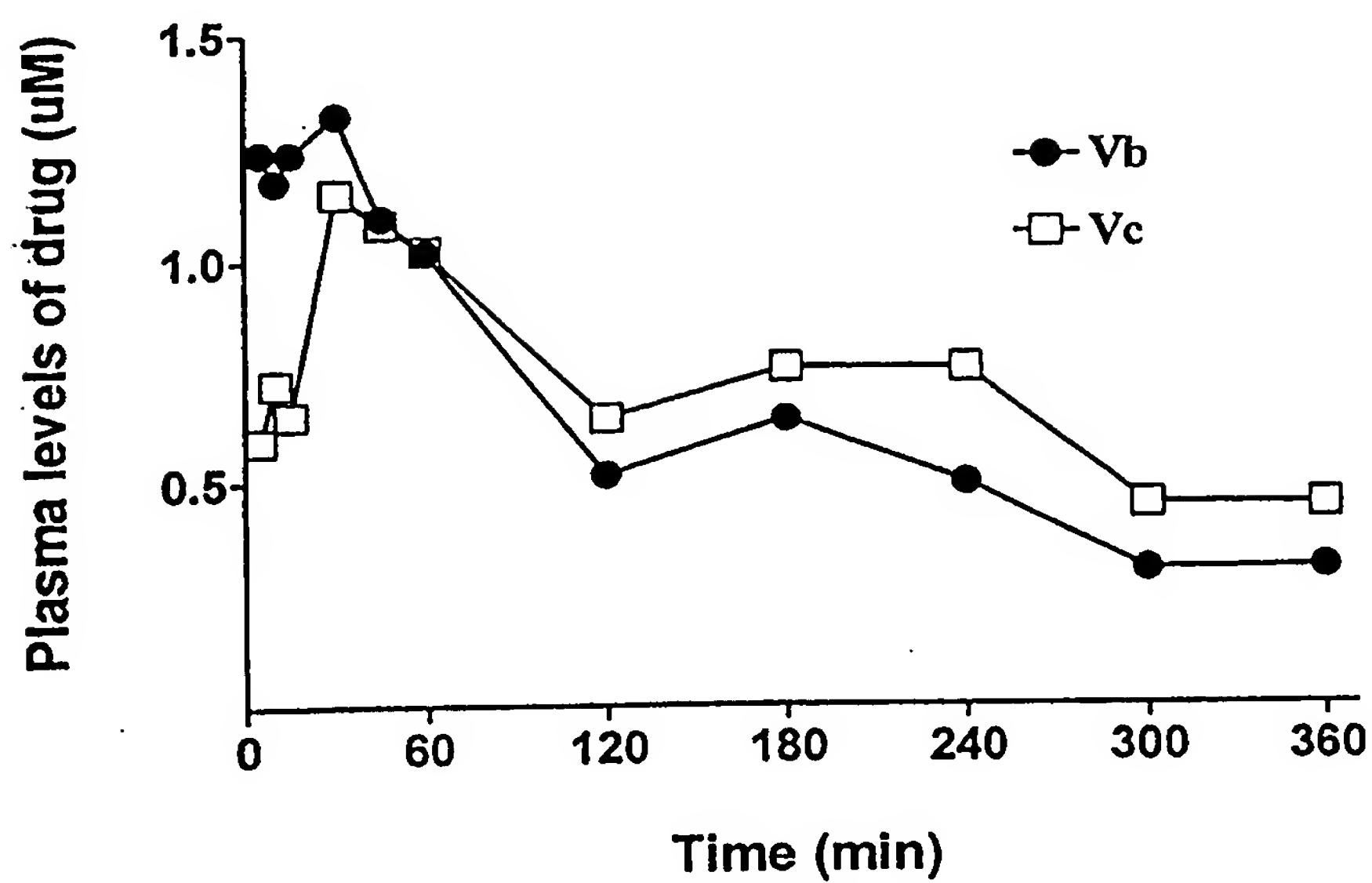
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FIGURE 19



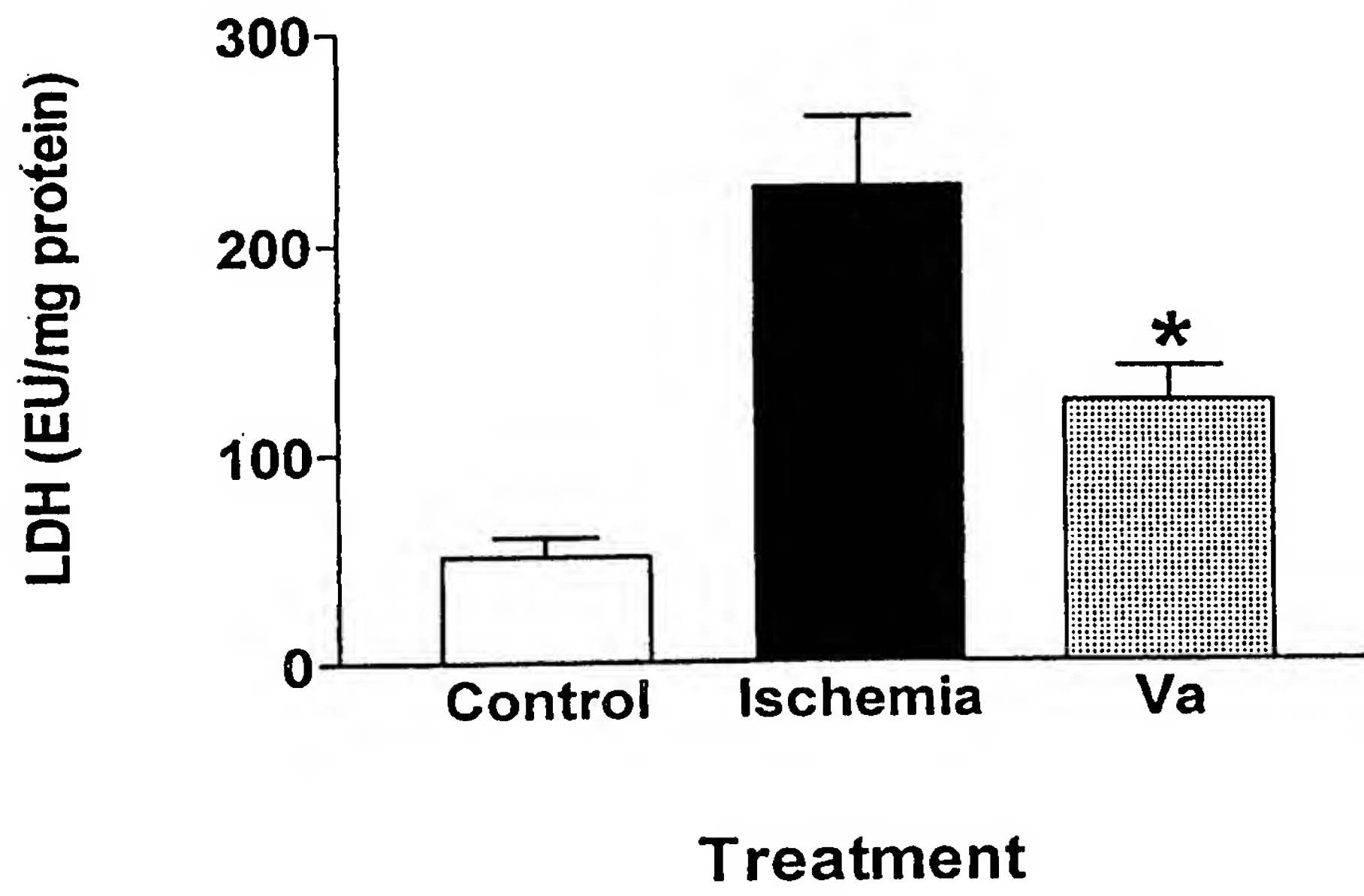
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FIGURE 20



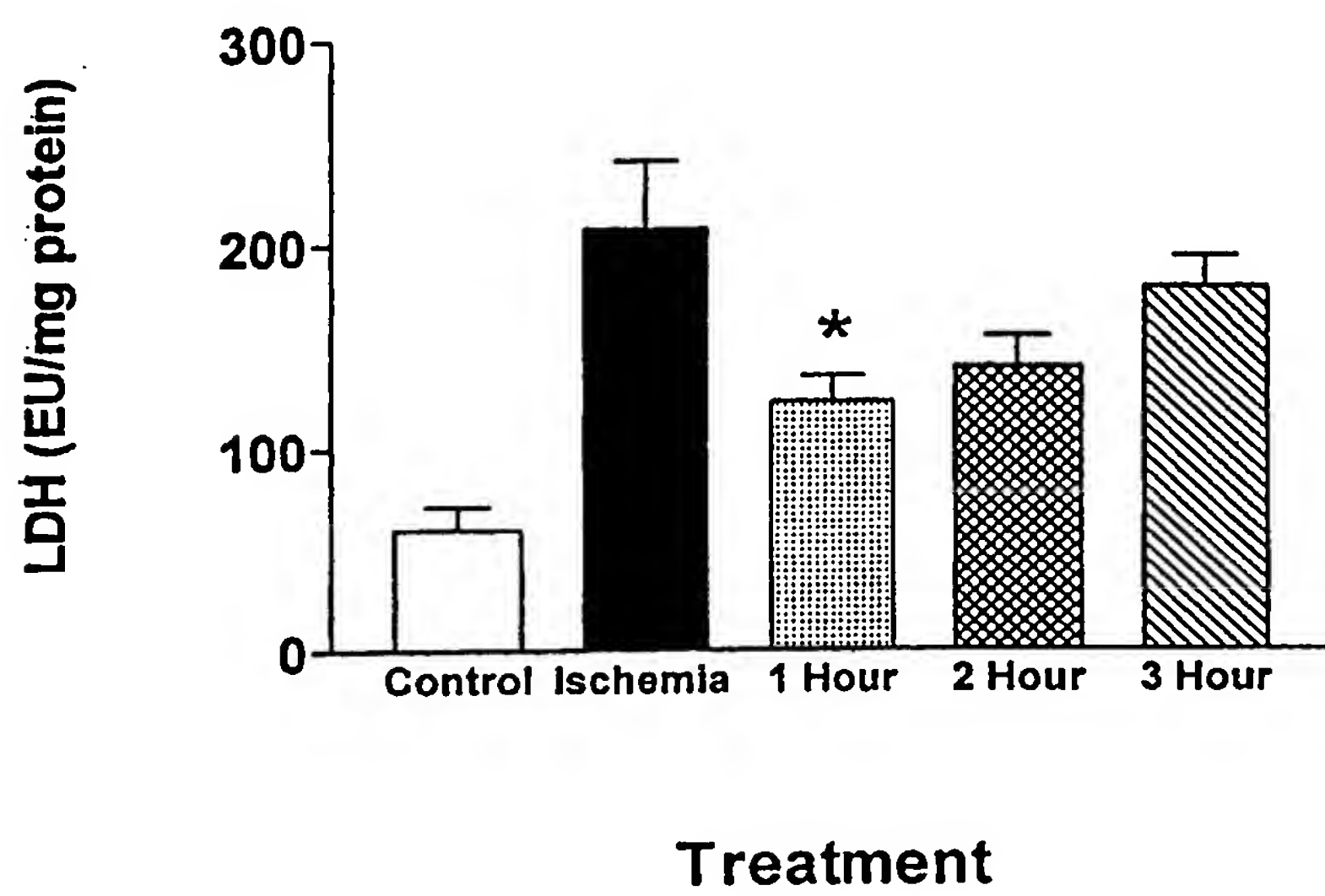
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FIGURE 21



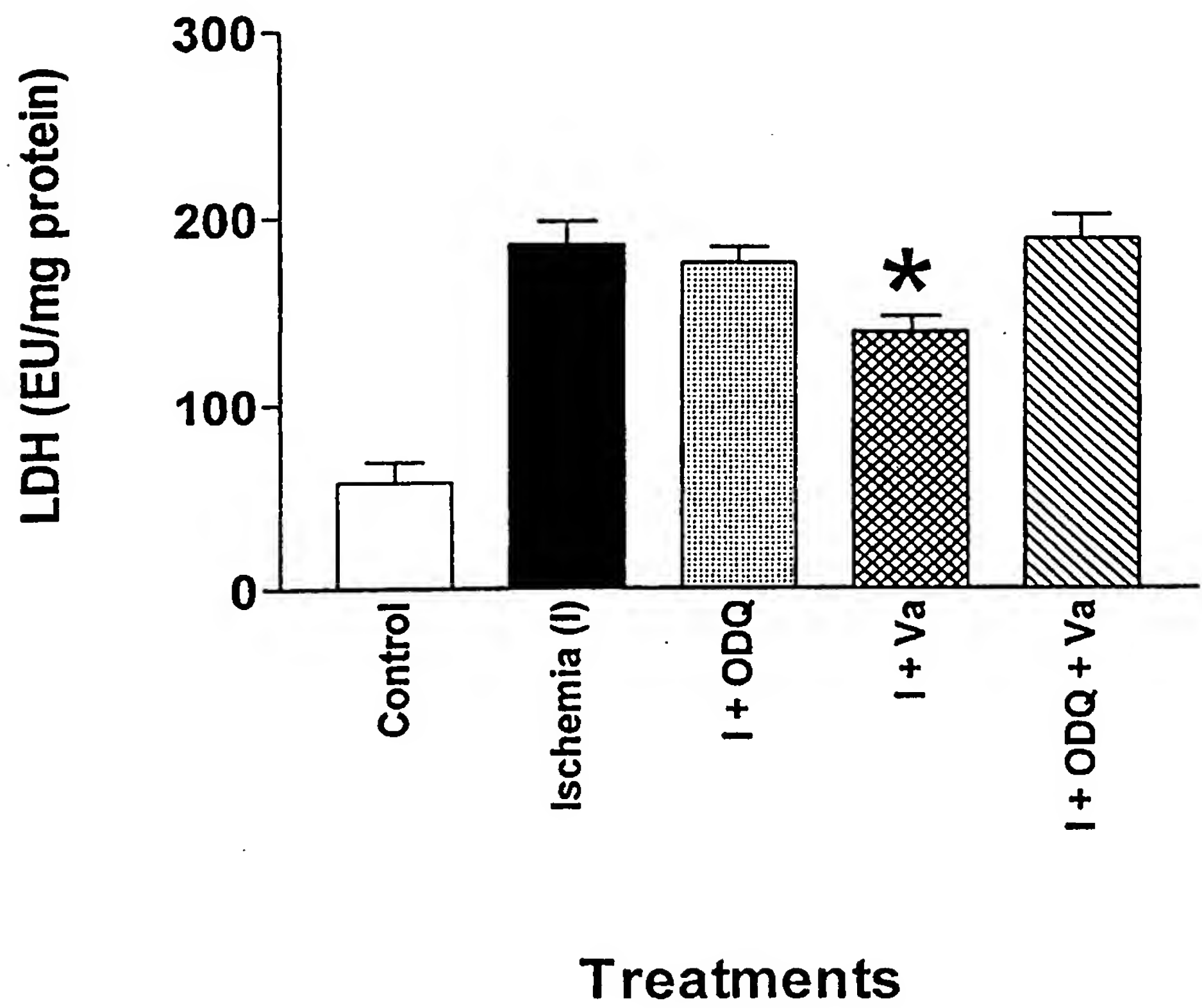
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FIGURE 22



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FIGURE 23



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FIGURE 24

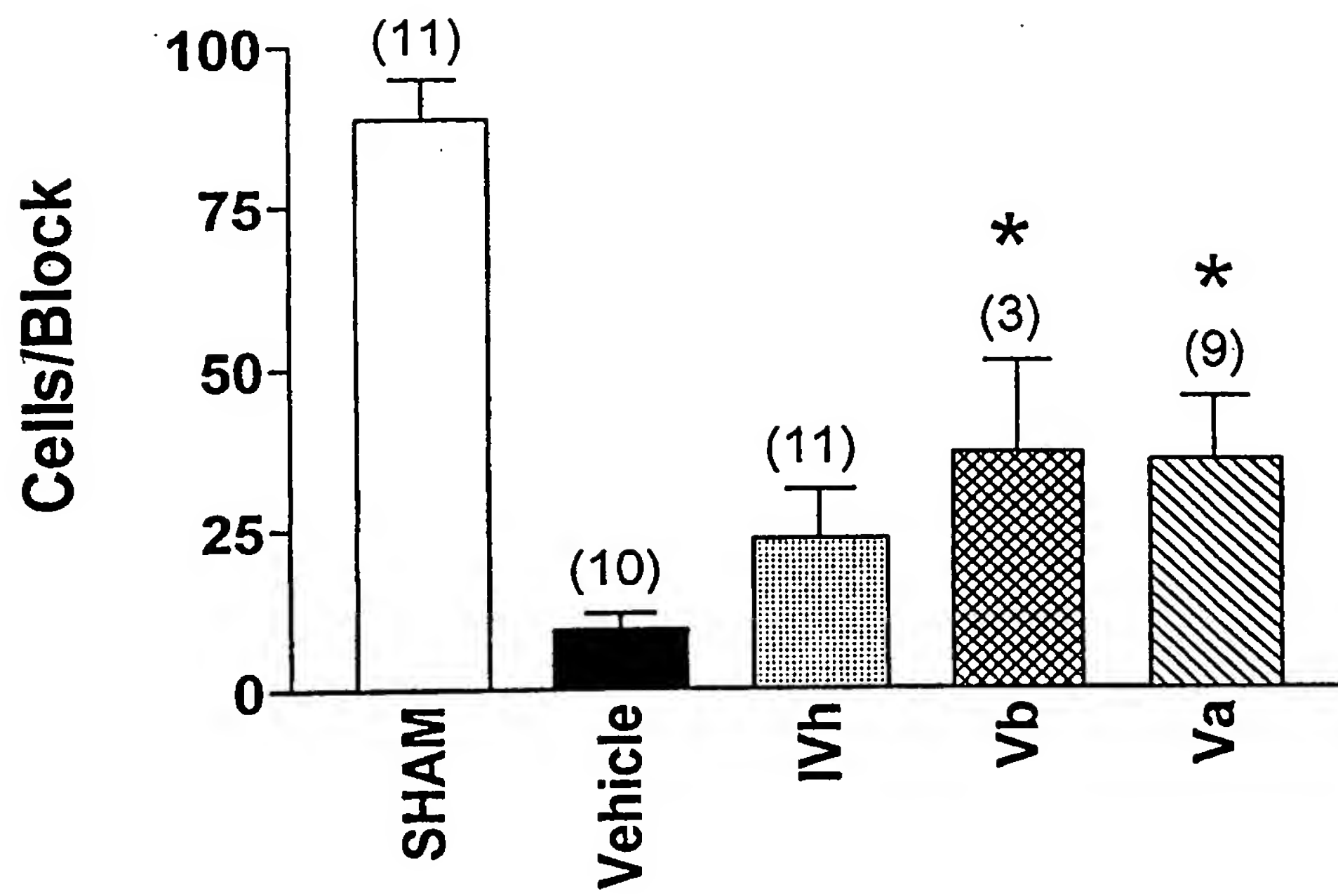
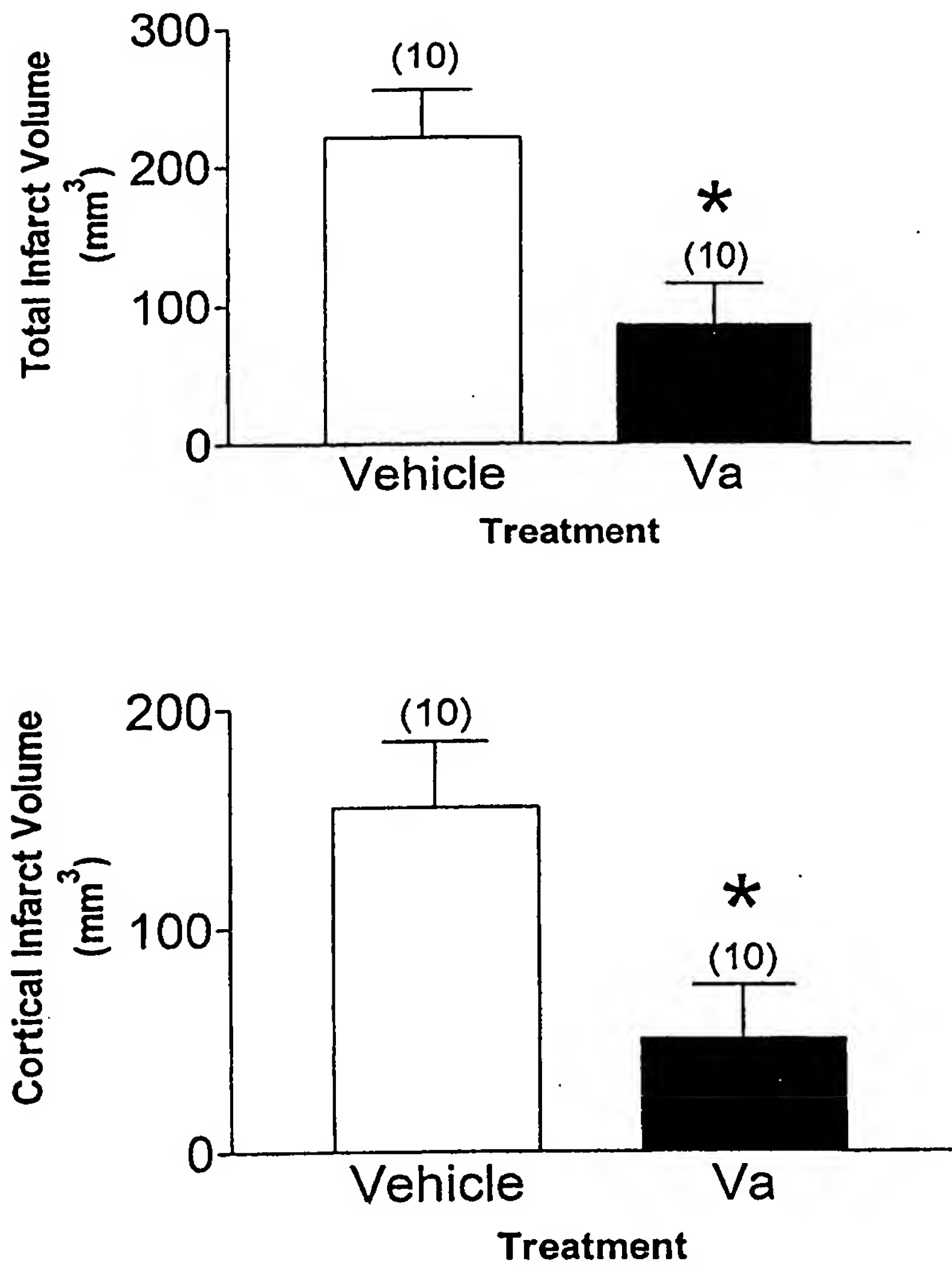
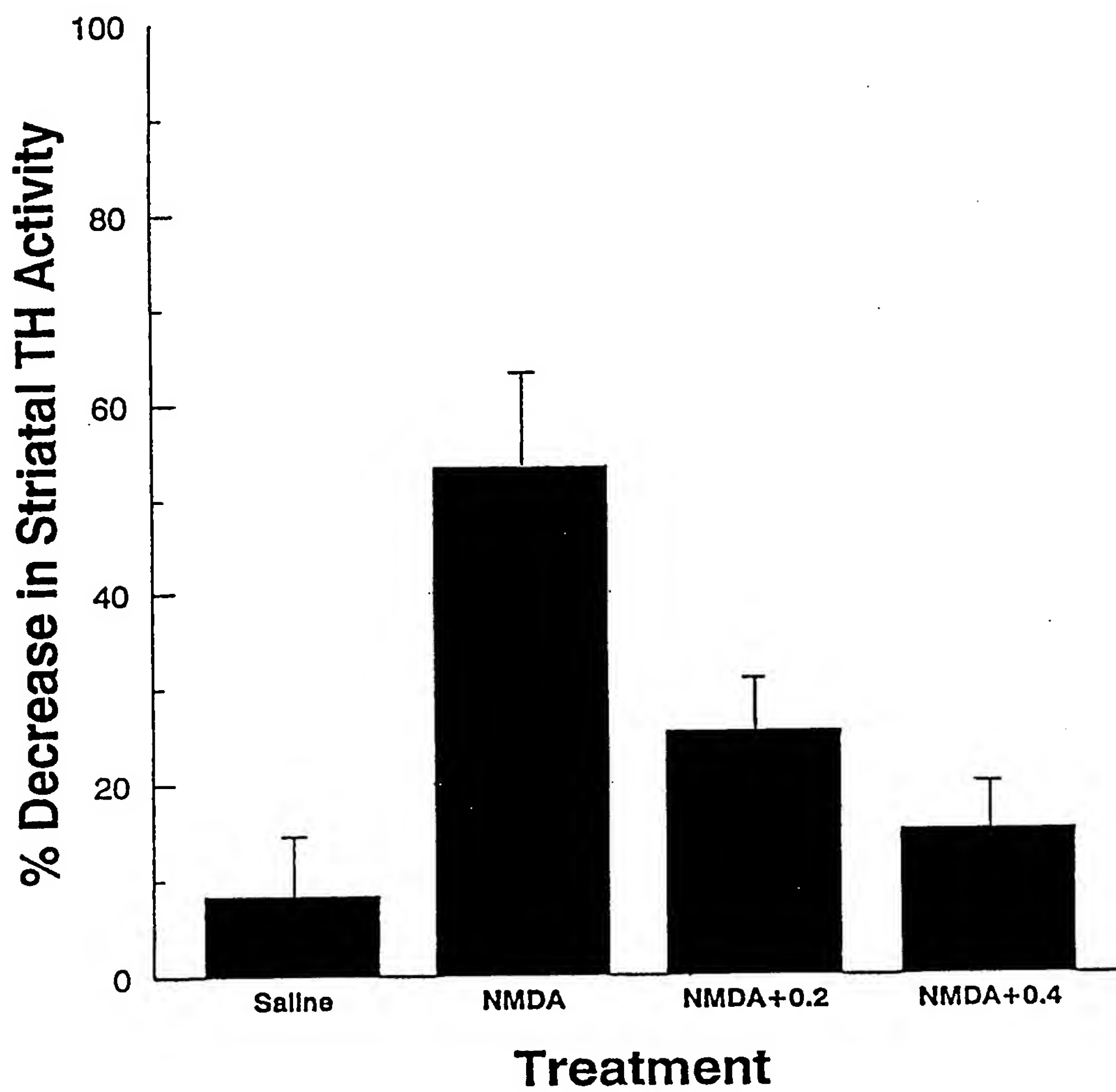


FIGURE 25



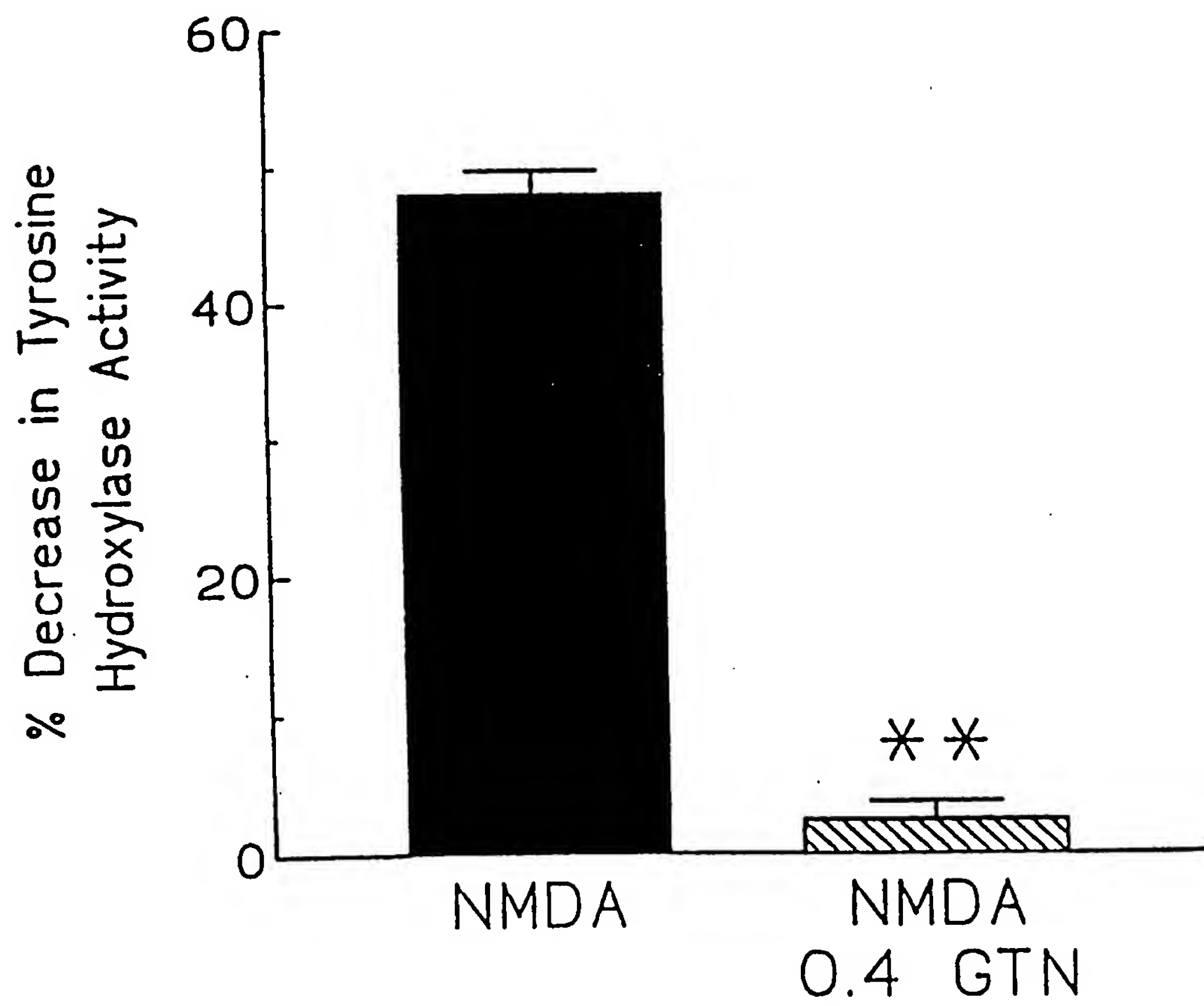
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FIGURE 26



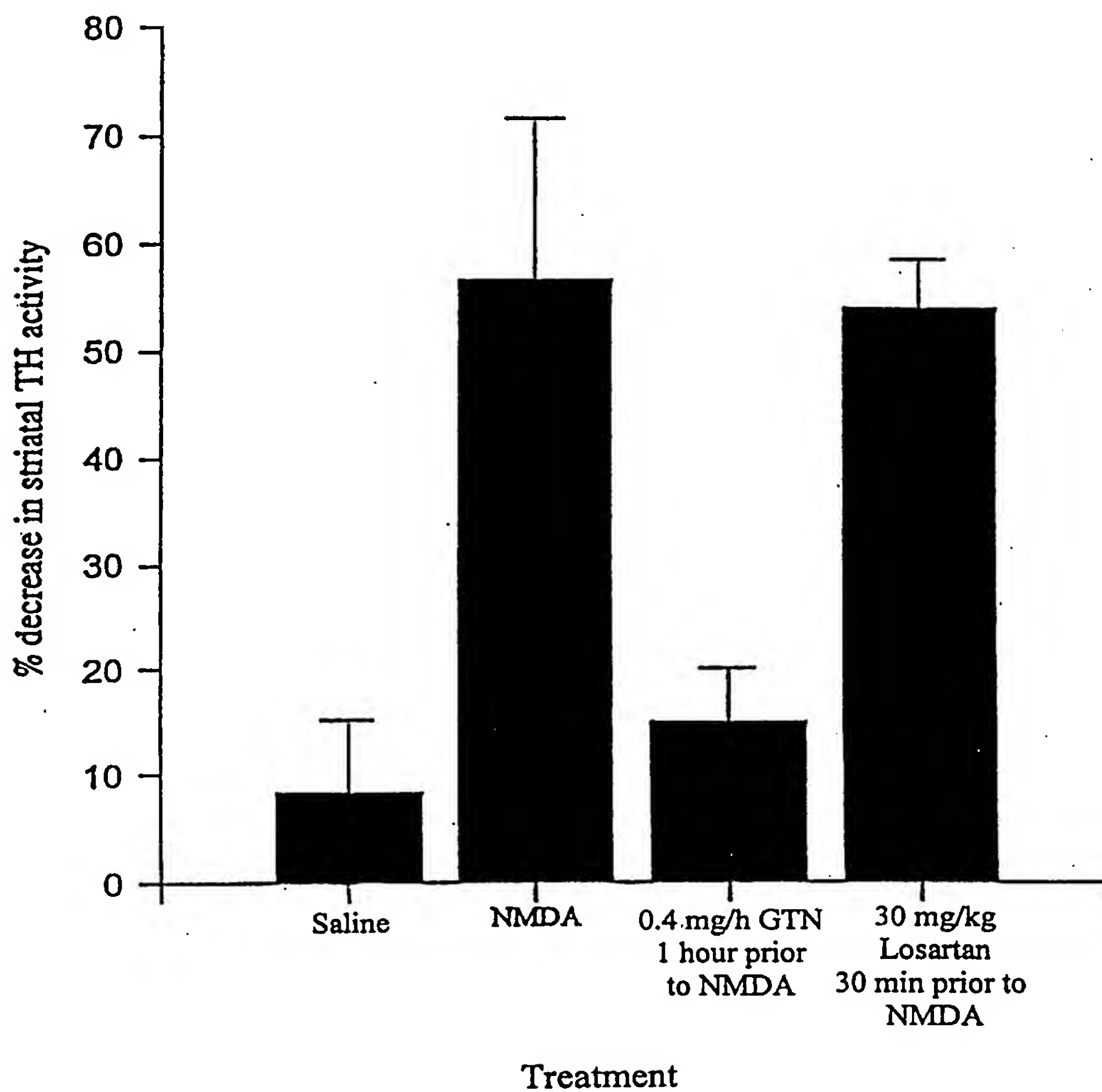
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FIGURE 27



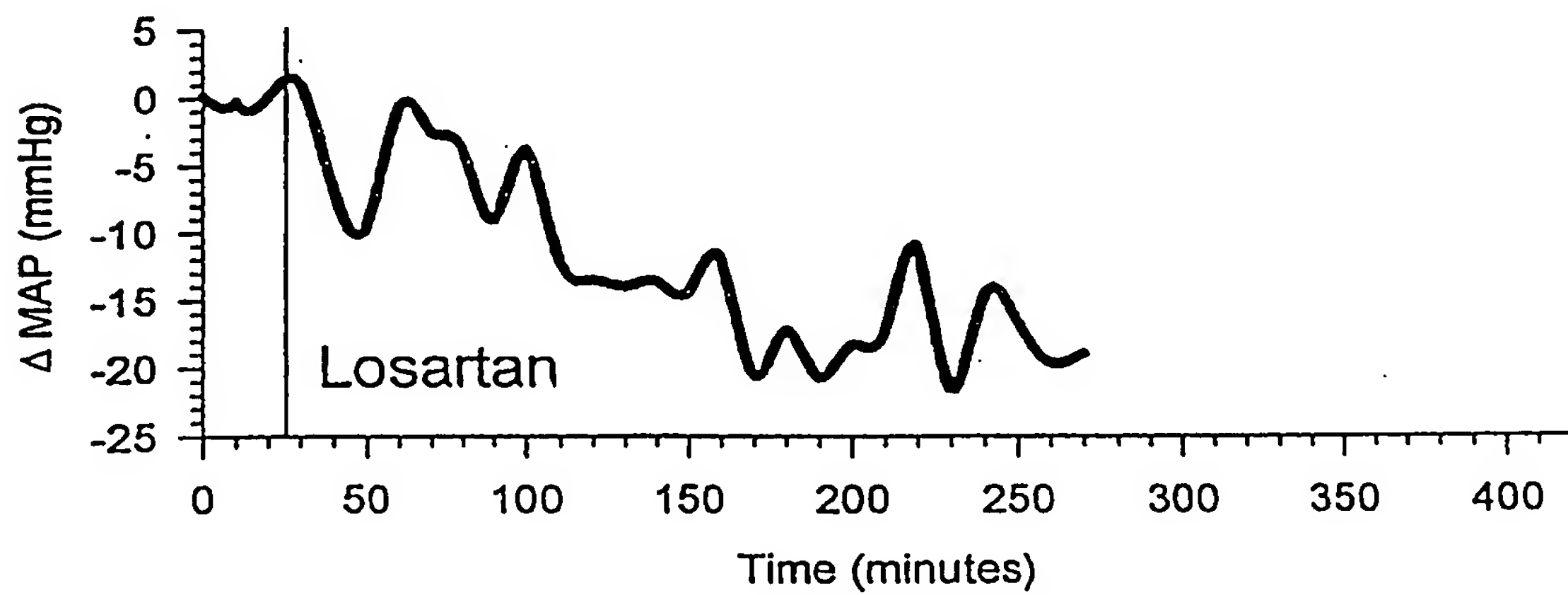
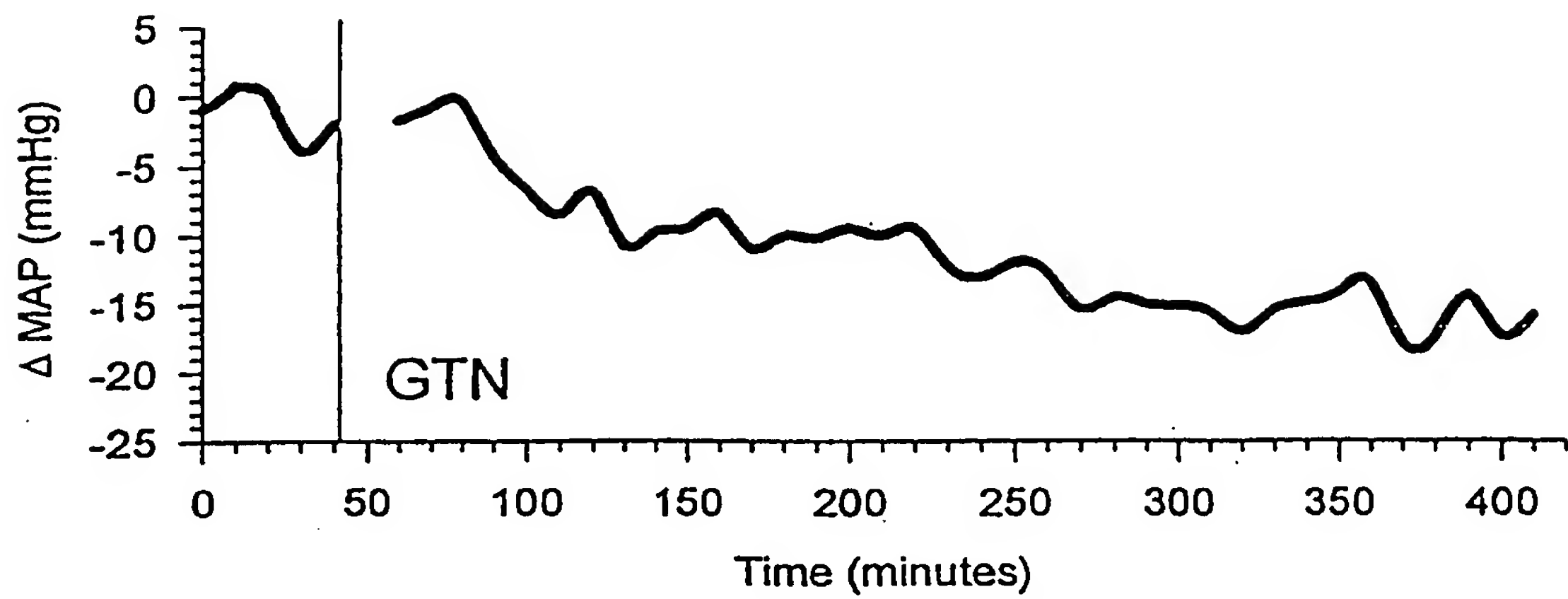
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FIGURE 28



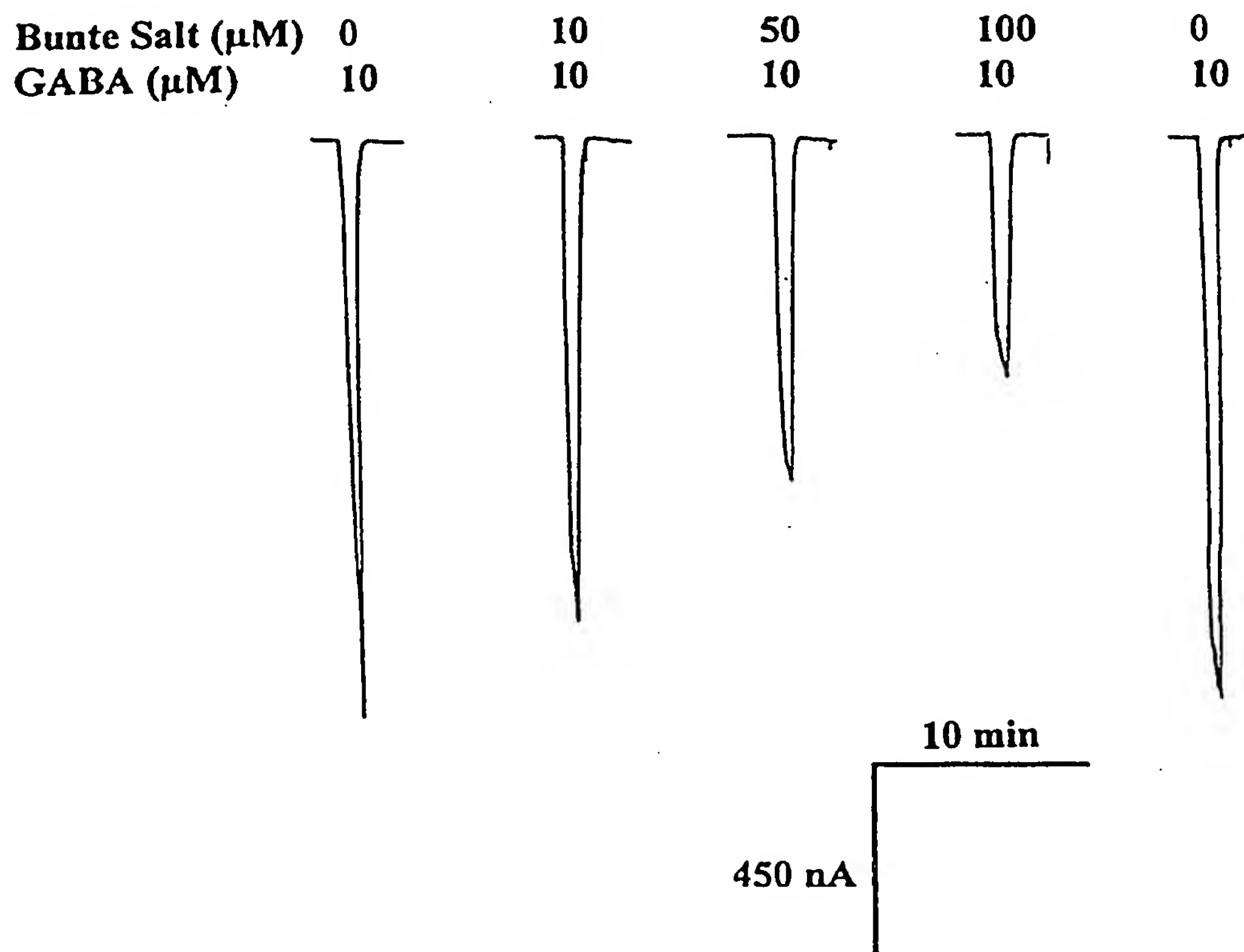
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FIGURE 29



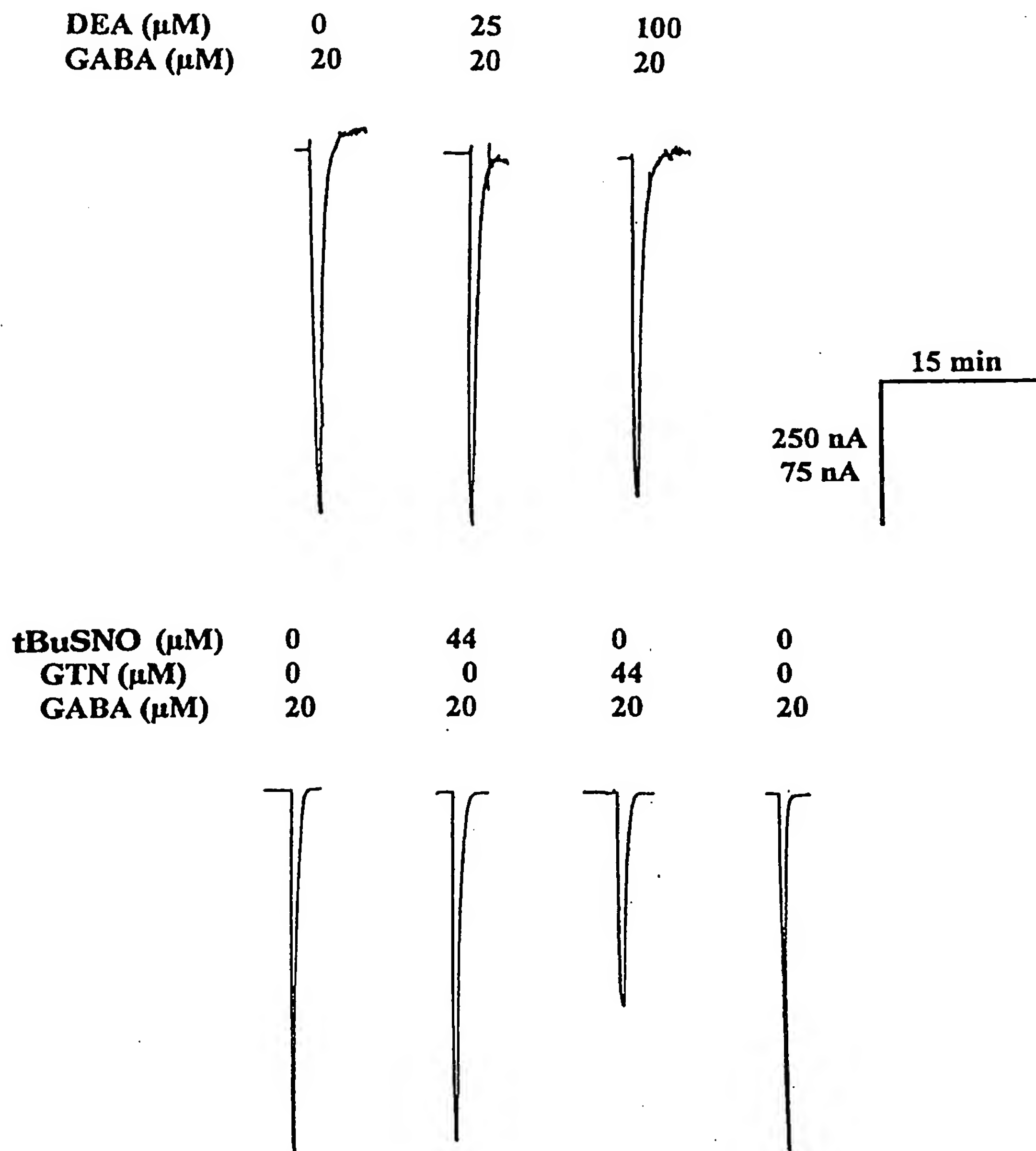
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FIGURE 30



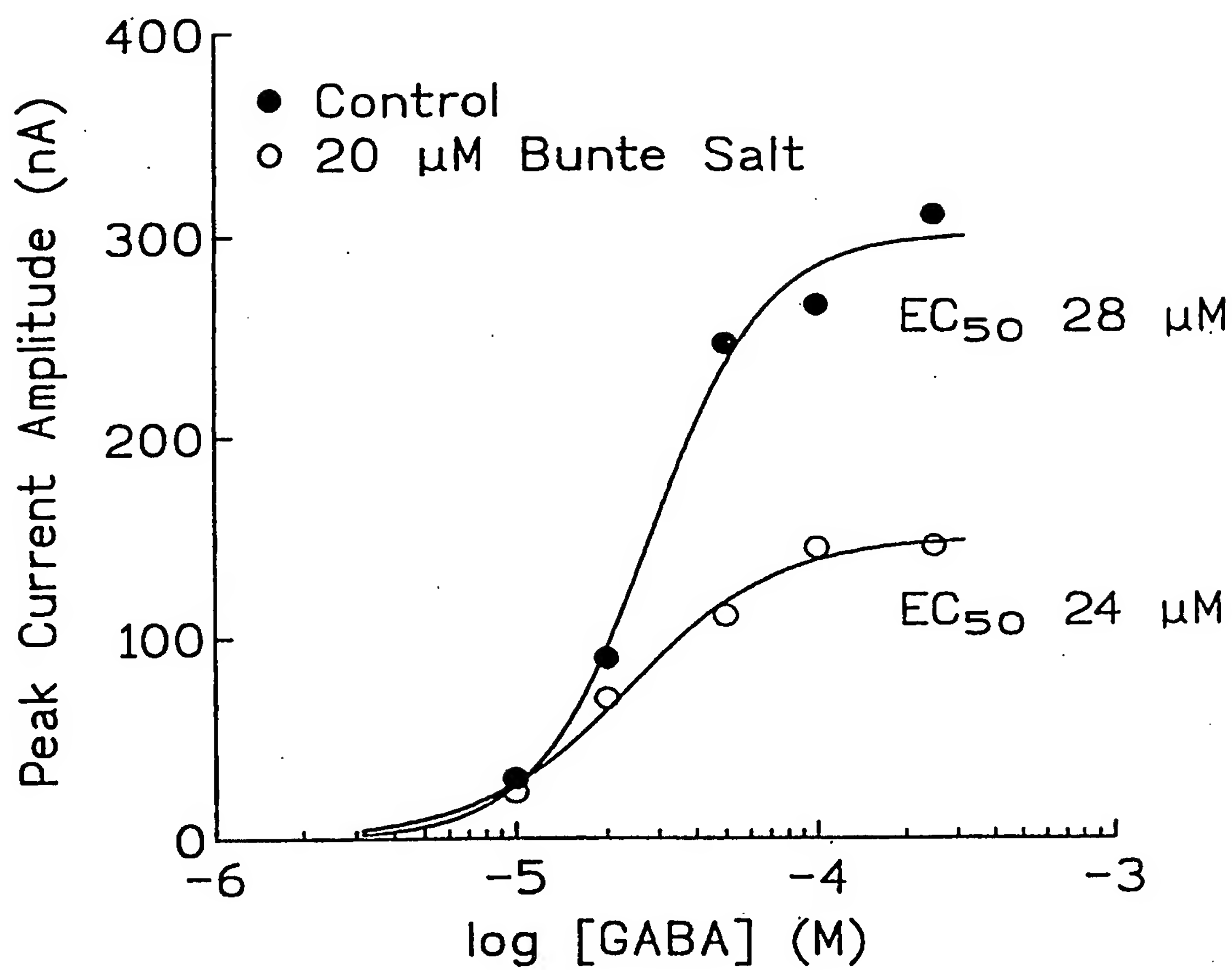
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FIGURE 31



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FIGURE 32



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<p>(51) International Patent Classification ⁷ : C07C 203/04, 327/34, C07D 209/28, 233/64, 495/04, C07C 211/49, C07F 9/38, C07D 295/088, 207/16, 499/32, 473/08, C07C 211/42, C07D 219/10, 307/30, 401/14, 401/12, 407/04, 417/12, C07H 15/252, A61K 31/21</p>	<p>A2</p>	<p>(11) International Publication Number: WO 00/61537 (43) International Publication Date: 19 October 2000 (19.10.00)</p>
<p>(21) International Application Number: PCT/EP00/03234 (22) International Filing Date: 11 April 2000 (11.04.00) (30) Priority Data: MI99A000753 13 April 1999 (13.04.99) IT (71) Applicant (for all designated States except US): NICOX S.A. [FR/FR]; 45 Avenue Kléber, F-75116 Paris (FR). (72) Inventor; and (75) Inventor/Applicant (for US only): DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I-20052 Monza (IT). (74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni 2, I-20129 Milano (IT).</p>	<p>(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.</p>	
<p>(54) Title: PHARMACEUTICAL COMPOUNDS</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> $A-(B)-C-N(O)_s \quad (I)$ </div> <div style="text-align: center;"> $\begin{array}{c} A-C_1-B_1 \\ \\ N(O)_s \end{array} \quad (II)$ </div> </div> <p>(57) Abstract</p> <p>Compounds or their salts having general formulas (I) and (II): wherein s is an integer equal to 1 or 2, preferably s = 2; A is the radical of a drug and is such as to meet the pharmacological tests reported in the description, C and C₁ are two bivalent radicals. The precursors of the radicals B and B₁ are such as to meet the pharmacological test reported in the description.</p>		

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"PHARMACEUTICAL COMPOUNDS"

* * * * *

The present invention relates to novel drugs for systemic use and non systemic use, and the composition thereof, to be used in oxidative stress and/or endothelial dysfunctions cases.

By oxidative stress it is meant the generation of free radicals or radicalic compounds, which causes injury both of the cell and that of the surrounding tissue (Pathophysiology: the biological basis for disease in adults and children, McCance & Huether 1998 pages 48-54).

By endothelial dysfunctions it is meant those relating to the vasal endothelium. The damage of the vasal endothelium is known as one of those important events that can cause a series of pathological processes affecting various organs and body apparatuses, as described hereinafter (Pathophysiology: The biological basis for disease in adults and children, McCance & Huether 1998 page 1025).

As known, the oxidative stress and/or the endothelial dysfunctions are associated to various pathologies as reported hereinafter. The oxidative stress can also be caused by toxicity of a great variety of drugs, which significantly affects their performances.

Said pathological events are of a chronic, debilitating character and are very often typical of the elderly . As already said, in said pathological conditions the drugs used show a remarkably worsened performance.

Examples of pathological situations caused by the oxidative stress and/or by the endothelial dysfunctions, or present in elderly, are the following:

- For the cardiovascular system: myocardial and vascular ischaemia in general, hypertension, stroke, arteriosclerosis, etc.
- For the connective tissue: rheumatoid arthritis and connected inflammatory diseases, etc.
- For the pulmonary system: asthma and connected inflammatory diseases, etc.
- For the gastrointestinal system: ulcerative and non ulcerative dyspepsias, intestinal inflammatory diseases, etc.
- For the central nervous system: Alzheimer disease, etc.
- For the urogenital system: impotence, incontinence.
- For the cutaneous system: eczema, neurodermatitis, acne.
- The infective diseases in general (ref.: Schwarz-KB, Brady "Oxidative stress during viral infection: A review" Free radical Biol. Med. 21/5, 641-649 1996).

Further the ageing process can be considered as a true pathologic condition (ref. Pathophysiology: the biological

basis for disease in adults and children, pages 71-77).

The known drugs when administered to patients having pathologies associated to oxidative stress and/or endothelial dysfunctions, show a lower activity and/or higher toxicity.

This happens for example for drugs such as the antiinflammatory, cardiovascular drugs, respiratory apparatus drugs, central nervous system drugs, bone system drugs, antibiotics, urogenital, endocrine drugs, etc.

Drug research is directed to find new molecules having an improved therapeutic index (efficacy/toxicity ratio) or a lower risk/benefit ratio, also for pathological conditions as those above mentioned, wherein the therapeutic index of a great number of drugs results lowered. In fact in the above mentioned conditions of oxidative stress and/or endothelial dysfunctions, many drugs show a lower activity and/or higher toxicity.

For instance antiinflammatory drugs, such as NSAIDs and anticolitic drugs, such as 5-aminosalicylic acid and its derivatives, show the following drawbacks. NSAIDs result toxic particularly when the organism is debilitated or affected by morbid conditions associated to oxidative stress. Said conditions are for example the following: age, pre-existing ulcer, pre-existing gastric bleeding, debilitating chronic diseases such as in particular those affecting cardiovascular, renal apparatuses, the haematic crisis, etc. ("Misoprostol reduces serious gastrointestinal complications in patients with

rheumatoid arthritis receiving non-steroidal anti-inflammatory drugs. A randomized, double blind, placebo-controlled trial." F.E. Silverstein et Al., Ann. Intern. Med. 123/4, 241-9, 1995; Martindale 31a ed. 1996, pag. 73, Current Medical Diagnosis and Treatment 1992, pages 431 and 794).

The administration of anti-inflammatory drugs to patients in the above mentioned pathological conditions can be made only at doses lower than those used in therapy in order to avoid remarkable toxicity phenomena. Thus anti-inflammatory activity results poor.

Beta-blockers, used for the angina, hypertension and cardiac arrhythmia treatment, show side effects towards the respiratory apparatus (dyspnoea, bronchoconstriction), and therefore they can cause problems in patients affected by pathologies to said organs (asthma, bronchitis). Therefore beta-blockers further worsen respiratory diseases such as asthma. Therefore in asthmatic patients reduced doses of said drugs must be used in order not to jeopardize even more the respiratory functionality. Thus the efficacy of the beta-blockers results very reduced.

Antithrombotics, such as for example dipyridamole, aspirin, etc., used for the prophylaxis of thrombotic phenomena, have the same drawbacks. In patients affected by pathologies connected to oxidative stress and/or endothelial dysfunctions, the therapeutic action or the tolerability of

these drugs, as in the case of aspirin, is greatly reduced.

Bronchodilators for example salbutamol, etc., are used in the asthma and bronchitis treatment and drugs active on the cholinergic system are used in pathologies such as urinary cholinergic incontinence. Their administration can produce similar side effects affecting the cardiovascular apparatus, causing problems both to cardiopathic and to hypertensive patients. Cardiopathies and hypertension are pathologies associated, as above said, to the oxidative stress and/or endothelial dysfunctions. Also these drugs show the same drawbacks as those above mentioned.

Expectorant and mucolytic drugs, which are used in the therapy of inflammatory states of the respiratory organs, show drawbacks in patients affected by the above described conditions. Their administration can give rise to heartburn and gastric irritability, particularly in the elderly.

Bone resorption inhibitors, such as diphosphonates (for example alendronate, etc.) are drugs showing high gastrointestinal toxicity. Therefore also these drugs can show the same drawbacks as those above mentioned.

Phosphodiesterase inhibitors, such as for example sildenafil, zaprinast, used in the cardiovascular and respiratory system diseases, are characterized by similar problems as to tolerability and/or efficacy in the mentioned pathological conditions of oxidative stress and/or endothelial

dysfunctions.

Antiallergic drugs, for example cetirizine, montelukast, etc. show similar problems in the mentioned pathological conditions, particularly for that it concerns their efficacy.

Anti-angiotensin drugs, f.i. ACE-inhibitors, for example enalapril, captopril, etc., and receptor inhibitors, for example losartan, etc., are used in the cardiovascular disease treatment. Their drawback is to give side effects to the respiratory apparatus (i.e. cough, etc.) in the above mentioned pathological conditions.

Antidiabetic drugs, both of the insulin-sensitizing and of hypoglycaemizing type, such as for example sulphonylureas, tolbutamide, glypiride, glyclazide, glyburide, nicotinamide etc., are ineffective in the prophylaxis of diabetic complications. Their administration can give side effects, such as for example gastric lesions. These phenomena become more intense in the pathological conditions above mentioned.

Antibiotics, for example ampicillin, clarithromycin, etc., and antiviral drugs, acyclovir, etc., show problems as regards their tolerability, for example they cause gastro-intestinal irritability.

Antitumoral drugs, for example doxorubicine, daunorubicin, cisplatinum, etc., have high toxicity, towards different organs, among which are stomach and intestine. Said toxicity is further worsened in the above mentioned pathologies of

oxidative stress and/or endothelial dysfunctions.

Antidementia drugs for example nicotine and colino-mimetics, are characterized by a poor tolerability especially in the above mentioned pathologies.

The need was felt to have available drugs showing an improved therapeutic performance, i.e. endowed both of a lower toxicity and/or higher efficacy, so that they could be administered to patients in morbid conditions of oxidative stress and/or endothelial dysfunctions, without showing the drawbacks of the drugs of the prior art.

It has now surprisingly and unexpectedly found that the aforementioned problems evidenced the administration of drugs, to patients affected by oxidative stress and/or endothelial dysfunctions, or to the elderly in general, are solved by a novel class of drugs as described hereinafter.

An object of the invention are compounds or their salts having the following general formulas (I) and (II):



wherein:

s = is an integer equal to 1 or 2, preferably s = 2;

A = R—T₁·, wherein

R is the drug radical and

T₁ = (CO)_t or (X)_t·, wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, or a free valence, t and t' are integers and equal to zero

or 1, with the proviso that $t = 1$ when $t' = 0$; $t = 0$ when $t' = 1$;

$B = -T_B-X_2-T_{BI}-$ wherein

T_B and T_{BI} are equal or different;

$T_B = (CO)$ when $t = 0$, $T_B = X$ when $t' = 0$, X being as above defined;

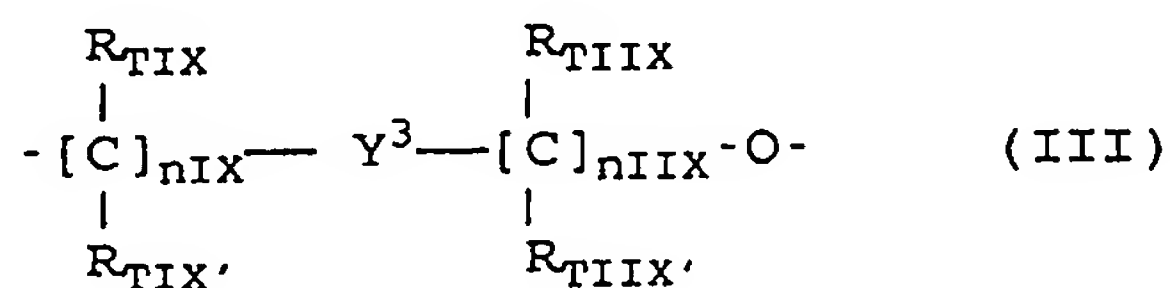
$T_{BI} = (CO)_{tx}$ or $(X)_{txx}$ wherein tx and txx have the 0 or 1 value; with the proviso that $tx = 1$ when $txx = 0$, and $tx = 0$ when $txx = 1$; X is as above defined;

X_2 is a bivalent bridging bond as defined below;

C is the bivalent $-T_C-Y-$ radical, wherein

$T_C = (CO)$ when $tx = 0$, $T_C = X$ when $txx = 0$, X being as above defined;

Y is an alkyleneoxy group $R'O$ wherein R' is linear or branched when possible C_1-C_{20} , preferably having from 1 to 6 carbon atoms, most preferably 2-4, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring may have side chains of R' type, R' being as above defined; or



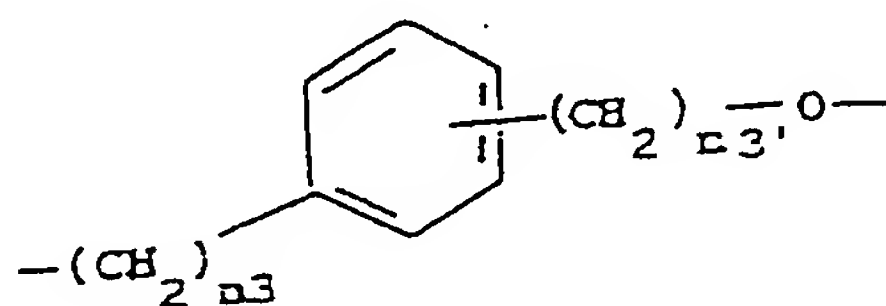
wherein:

nIX is an integer between 0 and 3, preferably 1;

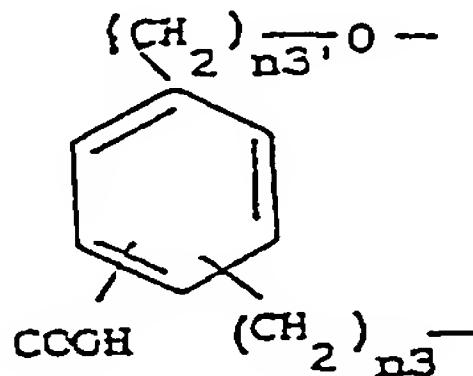
n_{IIX} is an integer between 1 and 3, preferably 1;

R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$, equal to or different from each other are H or a linear or branched C_1 - C_4 alkyl; preferably R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$ are H.

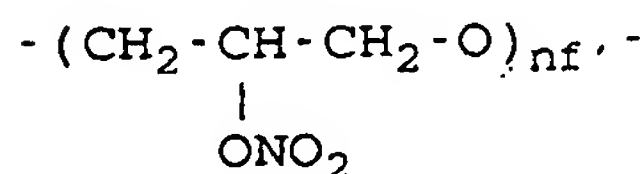
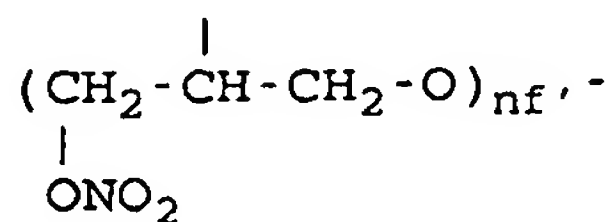
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen atom, preferably one or two nitrogen atoms, said ring having 5 or 6 atoms.



wherein n_3 is an integer from 0 to 3 and $n_{3'}$ is an integer from 1 to 3;

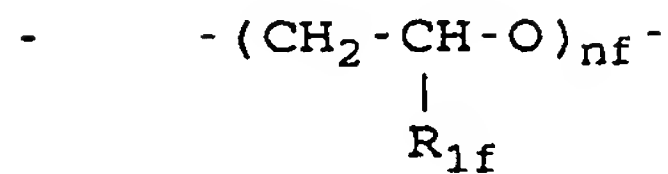
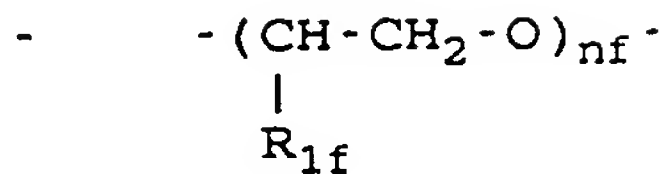


wherein n_3 and $n_{3'}$ have the above mentioned meaning



wherein $n_{f'}$ is an integer from 1 to 6 preferably from

1 to 4;



wherein $\text{R}_{1\text{f}} = \text{H}, \text{CH}_3$ and nf is an integer from 1 to

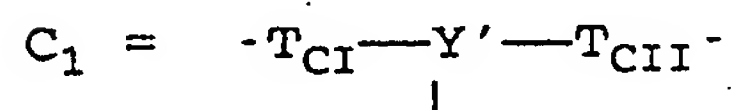
6; preferably from 1 to 4;

preferably $\text{Y} = -\text{R}'\text{O}-$ wherein R' is as above defined;

preferably R' is a $\text{C}_1\text{-C}_6$ alkylene;



wherein:

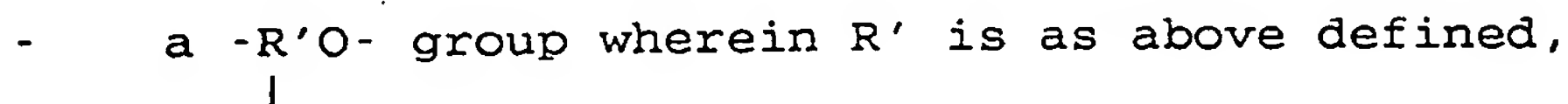


wherein T_{CI} and T_{CII} are equal or different,

$\text{T}_{\text{CI}} = (\text{CO})$ when $t = 0$, $\text{T}_{\text{CI}} = \text{X}$ when $t' = 0$, X being as above defined;

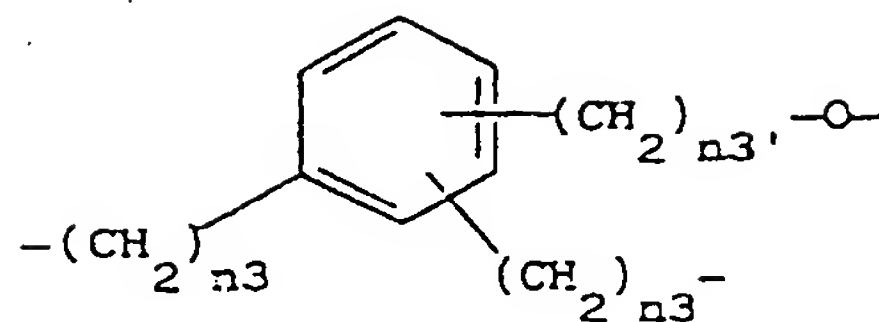
$\text{T}_{\text{CII}} = (\text{CO})_{t\text{I}}$ or $(\text{X})_{t\text{II}}$, wherein $t\text{I}$ and $t\text{II}$ have the 0 or 1 value; with the proviso that $t\text{I} = 1$ when $t\text{II} = 0$, and $t\text{I} = 0$ when $t\text{II} = 1$; X is as above defined;

Y' is as Y above defined, but with three free valences instead of two, preferably:

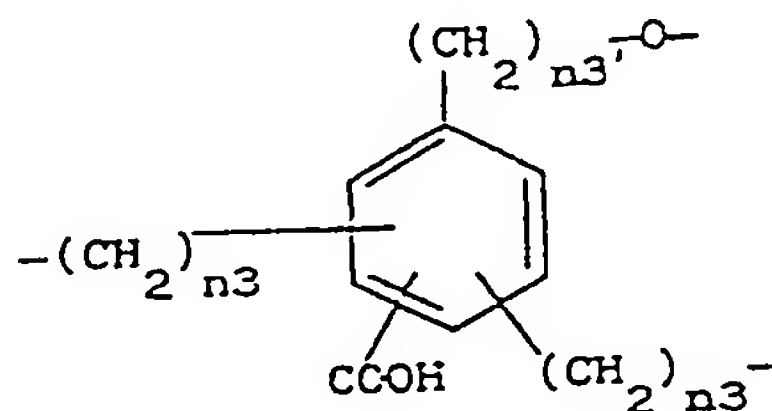


preferably from 1 to 6 carbon atoms, most preferably

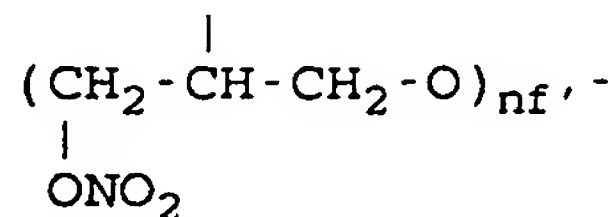
2-4, or



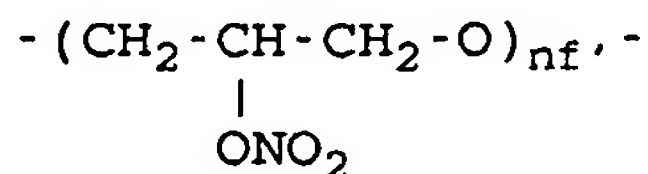
wherein n_3 is an integer from 0 to 3 and $n_{3'}$ is an integer from 1 to 3;



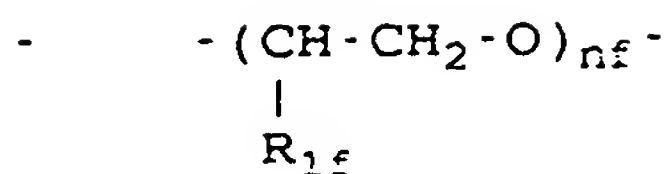
wherein n_3 and $n_{3'}$ have the above mentioned meaning;



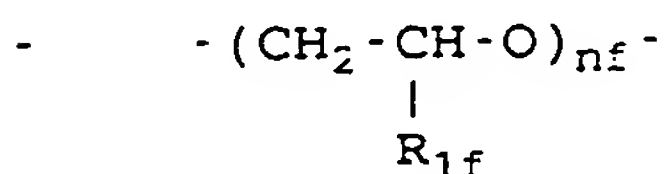
wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein nf' is an integer from 1 to 6 preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein $\text{R}_{1\text{f}} = \text{H}, \text{CH}_3$ and nf is an integer from 1 to 6; preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;

preferably $\text{Y}' = - \begin{array}{c} \text{R}'\text{O}- \\ | \end{array}$ wherein R' is a linear or

branched $\text{C}_2\text{-C}_4$, the oxygen which in Y' is covalently linked to the $-\text{N}(\text{O})_s$ group is at the end of the free bond indicated in C_1 formula;



wherein $\text{X}_{2\text{a}}$ is a monovalent radical as defined below,

$\text{T}_{\text{BII}} = (\text{CO})$ when $\text{tI} = 0$, $\text{T}_{\text{BII}} = \text{X}$ when $\text{tII} = 0$, X

being as above defined;

- X_2 , bivalent radical, is such that the corresponding precursor of B: $-\text{T}_{\text{B}}-\text{X}_2-\text{T}_{\text{BI}}-$ meets the test 4, precursor in which the T_{B} and T_{BI} free valence are each saturated with $-\text{OZ}$, $-\text{Z}$, or with $-\text{Z}^{\text{I}}-\text{N}-\text{Z}^{\text{II}}$, Z^{I} and Z^{II} being equal

or different and have the Z values as defined below, depending on the fact that T_{B} and/or $\text{T}_{\text{BI}} = \text{CO}$ or X , in

connection with the values of t , t' , tx and txx ;

- X_{2a} monovalent radical, such that the corresponding precursor of $B_1 - T_{BII} - X_{2a}$ meets the test 4, precursor wherein the free valence of T_{BII} is saturated with $-OZ$, $-Z$ or with $-Z^I-N-Z^{II}$, Z^I and Z^{II} being equal or different and having the Z values as defined below, depending on the fact that $T_{BII} = CO$ or X , in connection with the values of tI and tII ;
- the drug $A = R - T_1 -$, wherein the free valence is saturated as indicated hereinafter:

- when $t' = 0$ with:

- $O-Z$ wherein $Z = H$ or R_{1a} , R_{1a} being a linear or when possible branched C_1-C_{10} alkyl, preferably C_1-C_5 , or with Z^I-N-Z^{II} , Z^I and Z^{II} being as above defined,

- when $t = 0$ with $-Z$, wherein Z is as above defined,

with the proviso that the drug is not a steroid, is such to meet at least one of the tests 1-3;

- wherein test 1 (NEM) is a test in vivo carried out on four groups of rats (each formed by 10 rats), the controls (two groups) and the treated (two groups) of which one group of the controls and one group of the treated respectively are administered with one dose of 25 mg/kg s.c. of N-ethylmaleimide (NEM), the controls being treated with the carrier and the treated groups with the carrier + the drug of formula $A = R -$

T₁- wherein the free valence is saturated as above indicated, administering the drug at a dose equivalent to the maximum one tolerated by the rats that did not receive NEM, i.e. the highest dose administrable to the animal at which there is no manifest toxicity, i.e. such as to be symptomatologically observable; the drug complies with test 1, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in the group treated with NEM + carrier + drug are observed gastrointestinal damages greater than those of the group treated with the carrier, or of the group treated with the carrier + drug, or of the group treated with the carrier + NEM;

- wherein test 2 (CIP) is a test in vitro wherein human endothelial cells from the umbilical vein are harvested under standard conditions, then divided into two groups (each group replicated five times), of which one is treated with a mixture of the drug 10^{-4} M concentration in the culture medium, the other group with the carrier; then cumene hydroperoxide (CIP) having a 5 mM concentration in the culture medium is added to each of the two groups; the drug meets test 2, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), if a statistically significant inhibition of the apoptosis (cellular damage) induced by CIP is not obtained with $p < 0.01$ with respect to the group treated with the

carrier and CIP;

- wherein test 3 (L-NAME) is a test in vivo carried out on four groups of rats (each group formed by 10 rats) for 4 weeks and receiving drinking water, the controls (two groups) and the treated (two groups), of which one group of the controls and of the treated respectively receives in the above 4 weeks drinking water added of N- ω -nitro-L-arginine methyl ester (L-NAME) at a concentration of 400 mg/litre, the controls in the 4 weeks being administered with the carrier and the treated in the 4 weeks with the carrier + the drug, administering the carrier or the drug + carrier once a day, the drug being administered at the maximum dose tolerated by the group of rats not pretreated with L-NAME, i.e., the highest dose administrable to animals at which no manifest toxicity appears, i.e. such as to be symptomatologically observable; after the said 4 weeks, the water supply is stopped for 24 hours and then sacrificed, determining the blood pressure 1 hour before sacrifice, and after sacrifice of the rats determining the plasma glutamic pyruvic transaminase (GPT) after sacrifice, and examining the gastric tissue; the drug meets test 3, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when in the group of rats treated with L-NAME + carrier + drug, greater hepatic damages (determined as higher values of GPT) and/or gastric and/or cardiovascular damages (determined as higher values of blood-pressure) are found in comparison in

comparison respectively with the group treated with the carrier alone, or with the group treated with the carrier + drug, or with the group treated with the carrier + L-NAME;

- the precursors of B or B₁ with the free valences saturated as above defined must meet test 4: it is an analytical determination carried out by adding portions of methanol solutions of the precursor of B or B₁ at a 10⁻⁴ M concentration, to a methanol solution of DPPH (2,2-diphenyl-1-picryl hydrazyl - free radical); after having maintained the solution at room temperature away from light for 30 minutes, it is read the absorbance at the wave length of 517 nm of the test solution and of a solution containing only DPPH in the same amount as in the test solution; and then the inhibition induced by the precursor towards the radical production by DPPH is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

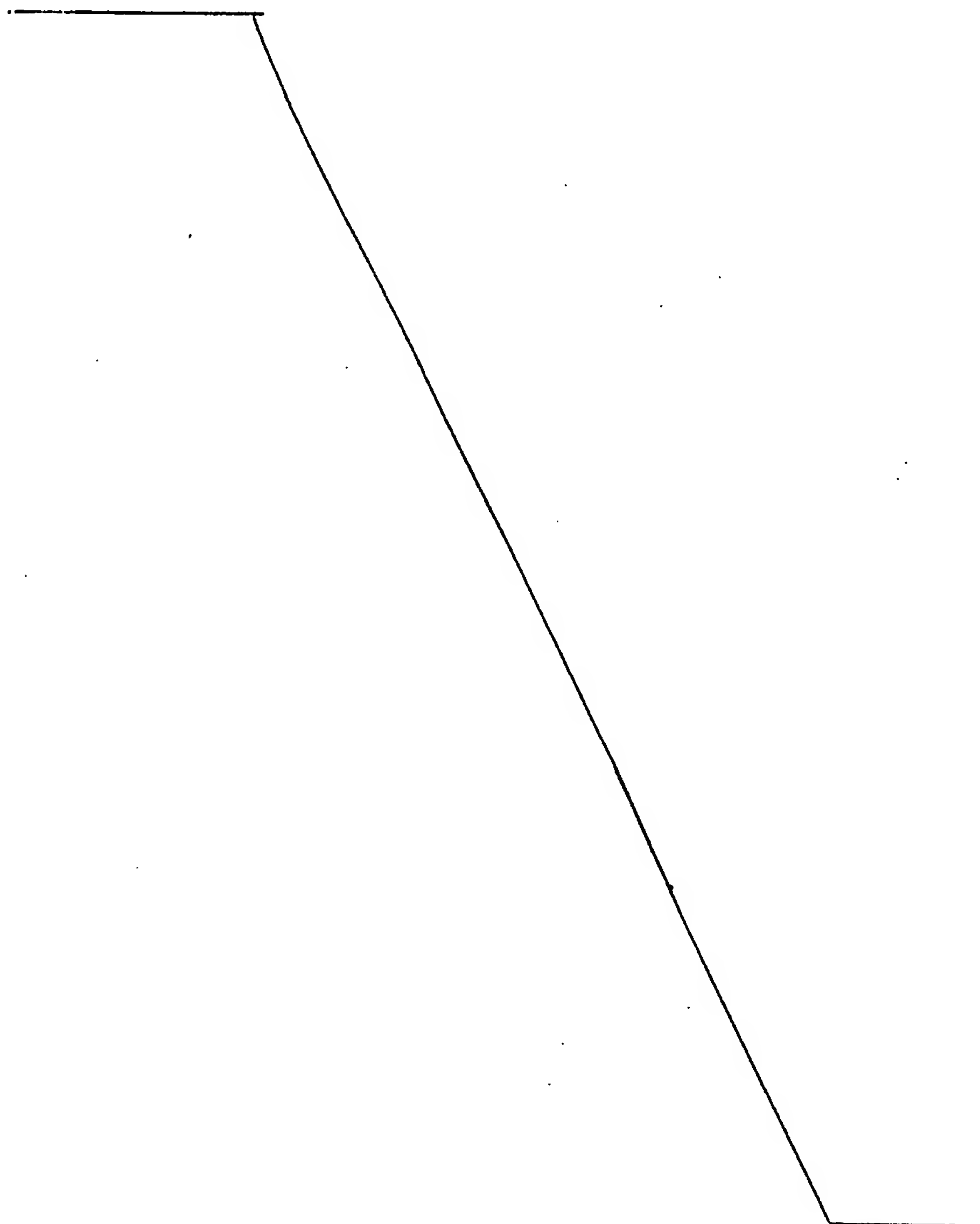
wherein A_s and A_c are respectively the absorbance values of the solution containing the test compound + DPPH and that of the solution containing only DPPH;

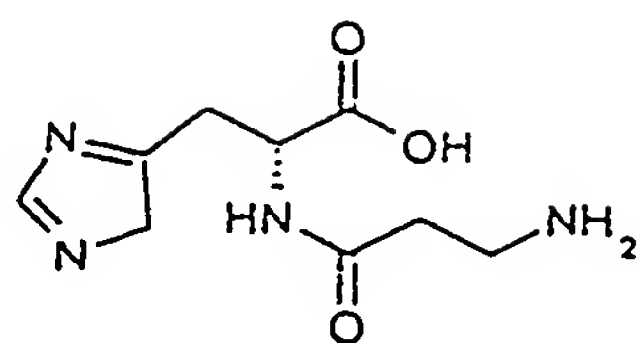
the precursor complies with test 4 when the percentage of inhibition as above defined is equal to or higher than 50%.

Preferably the precursor compound of B or B₁ (precursor of the X₂ or X_{2a} radical in the formulas (I) and (II) respectively), is selected from the following classes of compounds:

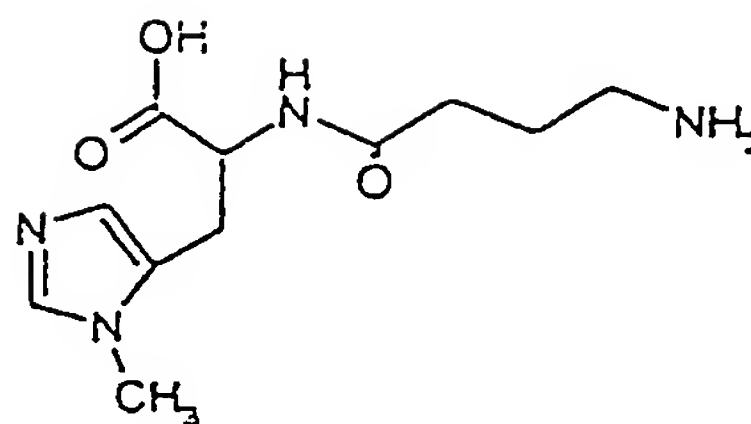
- Aminoacids, selected from the following: L-carnosine

(formula CI), anserine (CII), selenocysteine (CIII), selenomethionine (CIV), penicillamine (CV), N-acetylpenicillamine (CVI), cysteine (CVII), N-acetylcysteine (CVIII), glutathione (CIX) or its esters, preferably ethyl or isopropyl ester:

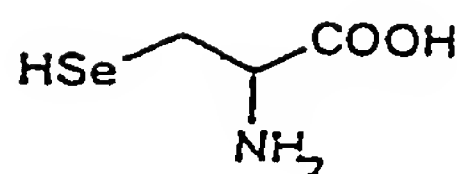




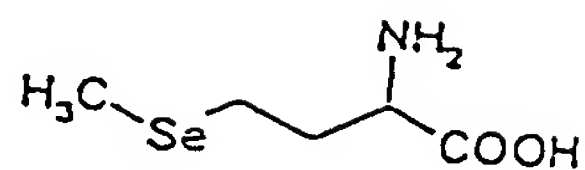
(CI)



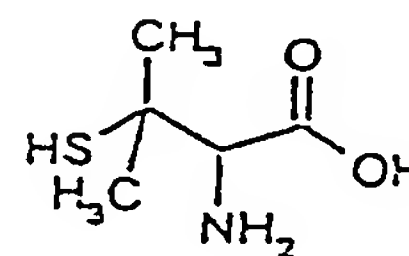
(CII)



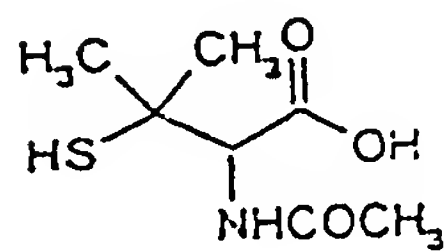
(CIII)



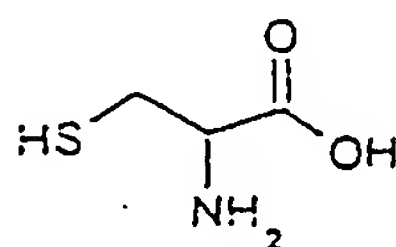
(CIV)



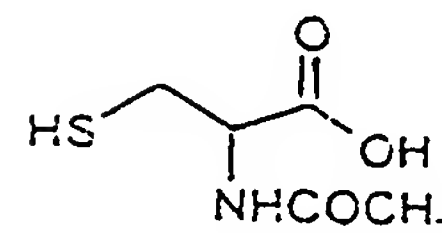
(CV)



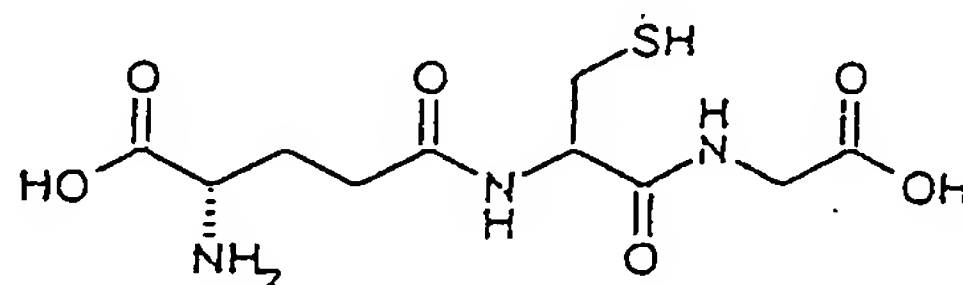
(CVI)



(CVII)



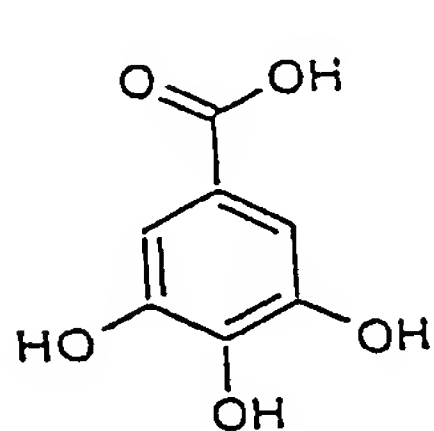
(CVIII)



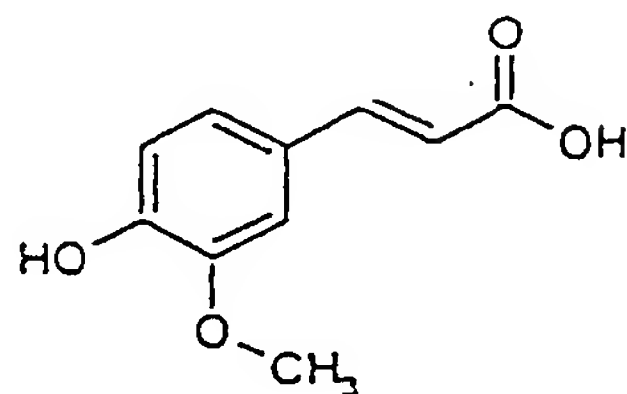
(CIX)

hydroxyacids, selected from the following: gallic acid (formula DI), ferulic acid (DII), gentisic acid (DIII), citric acid (DIV), caffeic acid (DV), hydro

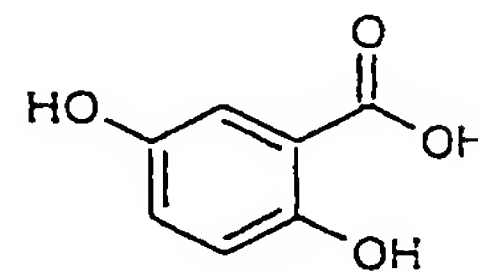
caffeic acid (DVI), p-coumaric acid (DVII), vanillic acid (DVIII), chlorogenic acid (DIX), kynurenic acid (DX), syringic acid (DXI):



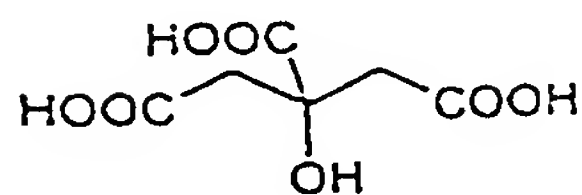
(DI)



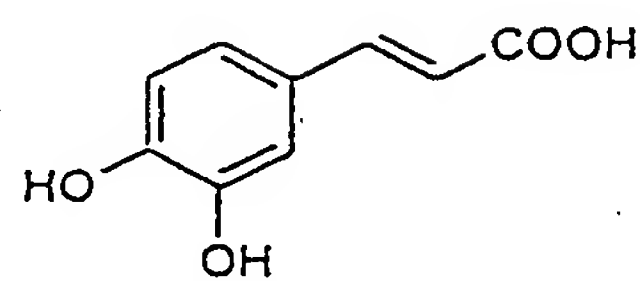
(DII)



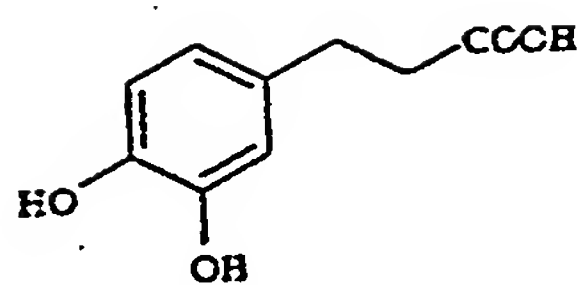
(DIII)



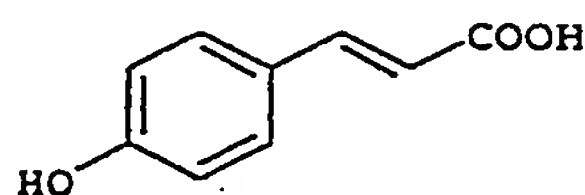
(DIV)



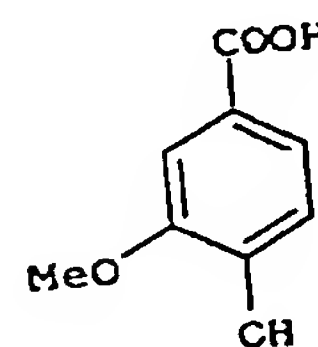
(DV)



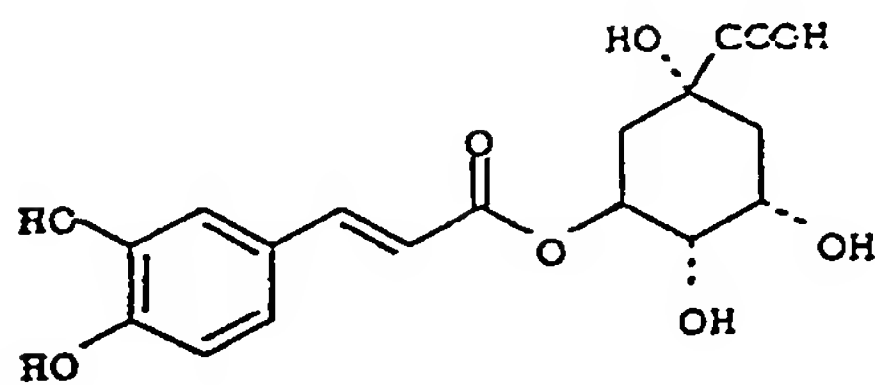
(DVI)



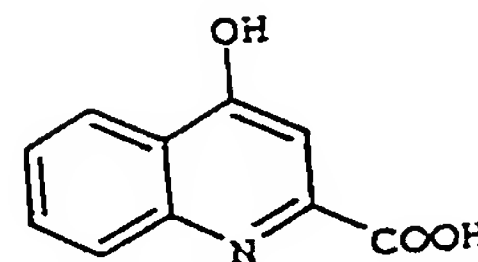
(DVII)



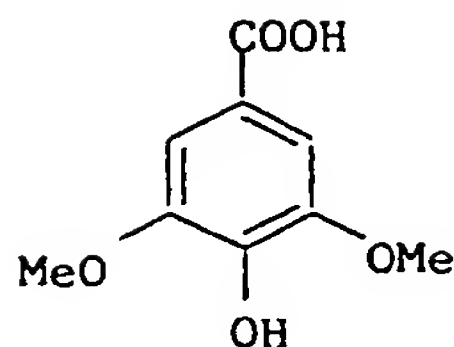
(DVIII)



(DIX)

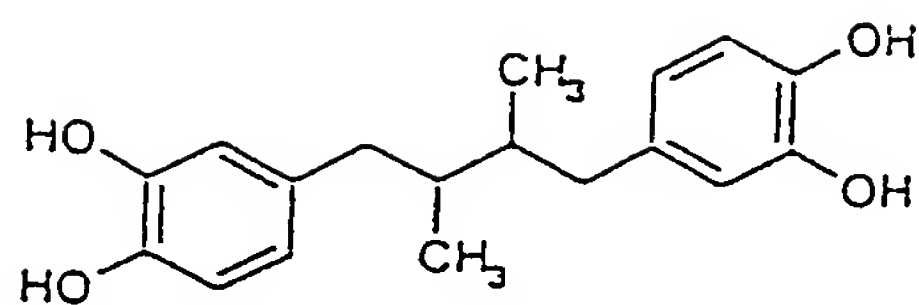


(DX)

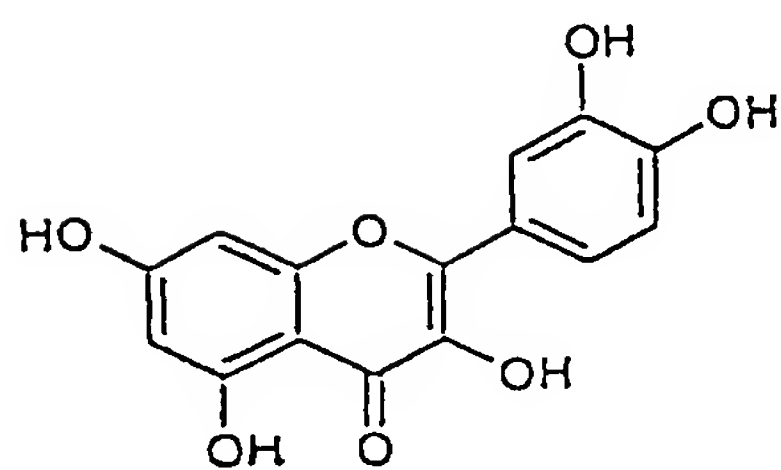


(DXI)

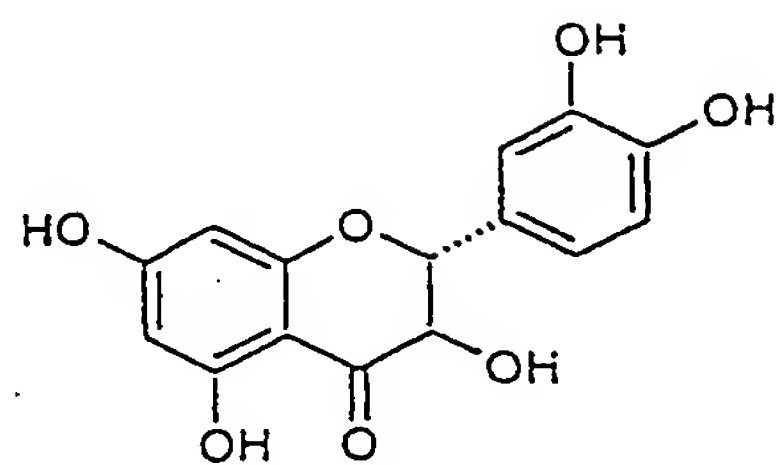
- Aromatic and heterocyclic mono- and polyalcohols, selected from the following: nordihydroguaiaretic acid (EI), quercetin (EII), catechin (EIII), kaempferol (EIV), sulphurethyne (EV), ascorbic acid (EVI), isoascorbic acid (EVII), hydroquinone (EVIII), gossypol (EIX), reductic acid (EX), methoxyhydroquinone (EXI), hydroxyhydroquinone (EXII), propyl gallate (EXIII), saccharose (EXIV), vitamin E (EXV), vitamin A (EXVI), 8-quinolol (EXVII), 3-ter-butyl-4-hydroxyanisole (EXVIII), 3-hydroxyflavone (EXIX), 3,5-ter-butyl-p-hydroxytoluene (EXX), p-ter-butyl phenol (EXXI), timolol (EXXII), xibornol (EXXIII), 3,5-di-ter-butyl-4-hydroxybenzyl-thioglycolate (EXXIV), 4'-hydroxybutyranilide (EXXV), guaiacol (EXXVI), tocol (EXXVII), isoeugenol (EXXVIII), eugenol (EXXIX), piperonyl alcohol (EXXX), allopurinol (EXXXI), conyferyl alcohol (EXXXII), 4-hydroxyphenetyl alcohol (EXXXIII), p-coumaric alcohol (EXXXIV), curcumin (EXXXV):



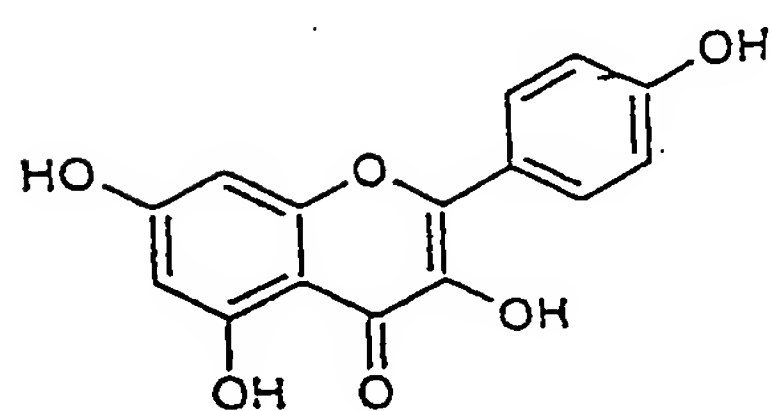
(EI)



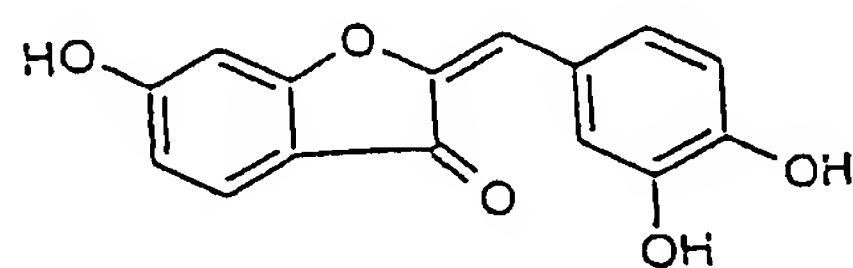
(EII)



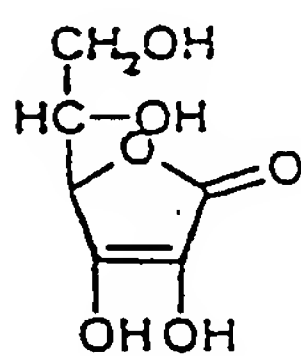
(EIII)



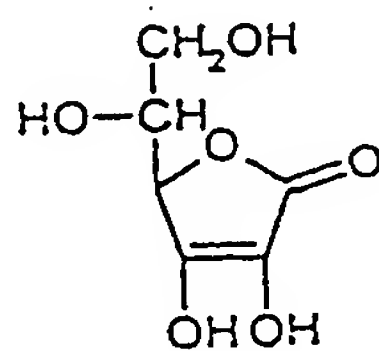
(EIV)



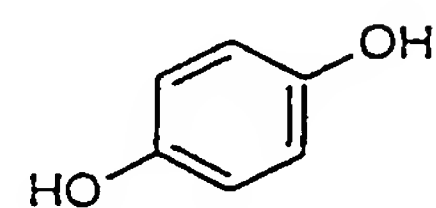
(EV)



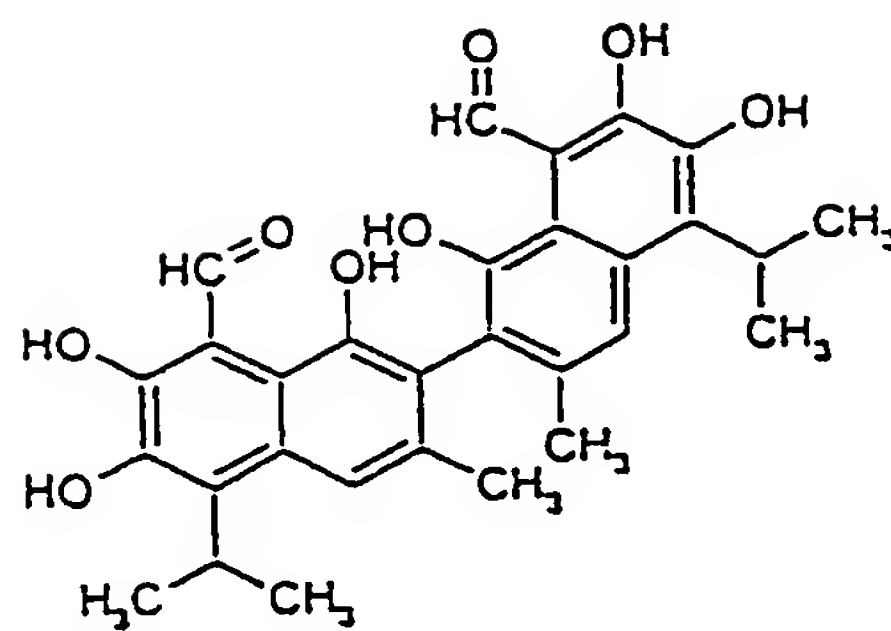
(EVI)



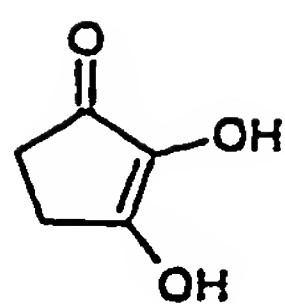
(EVII)



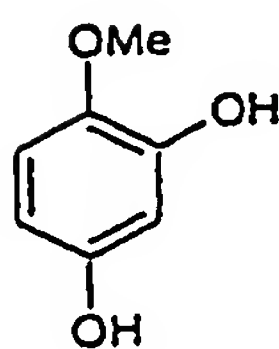
(EVIII)



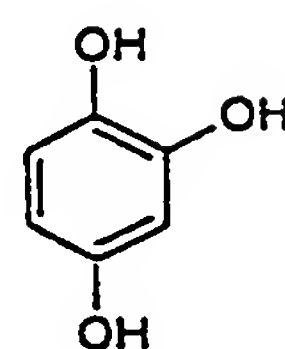
(EIX)



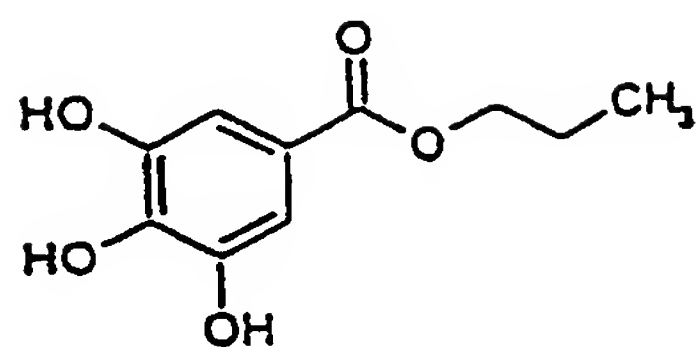
(EX)



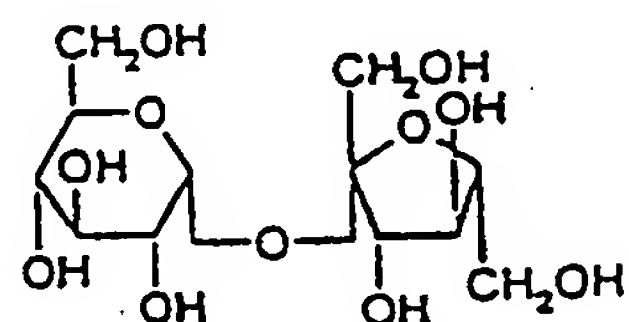
(EXI)



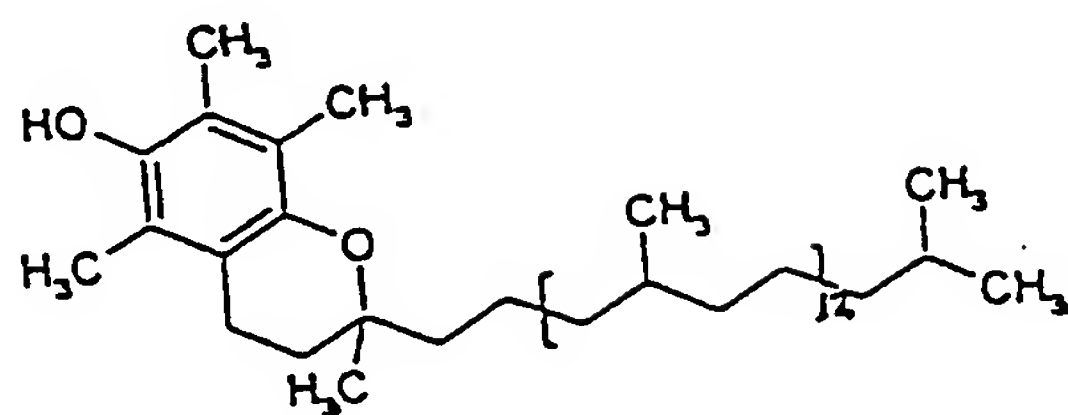
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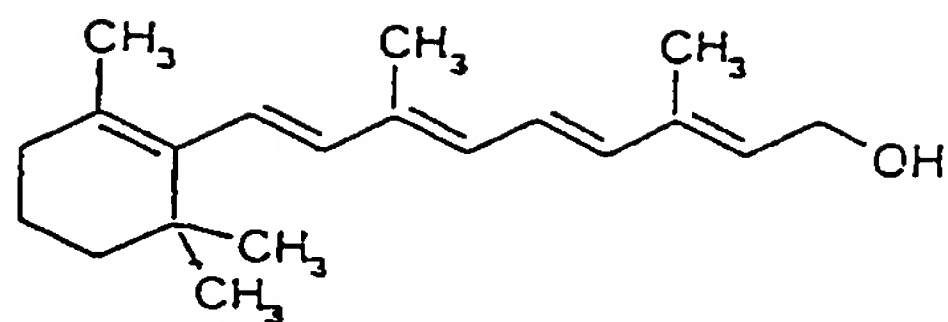
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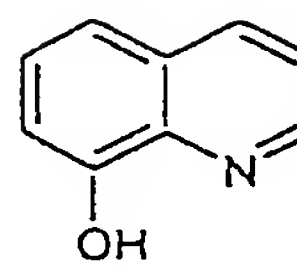
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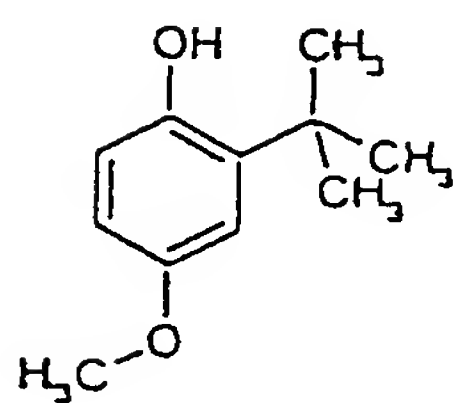
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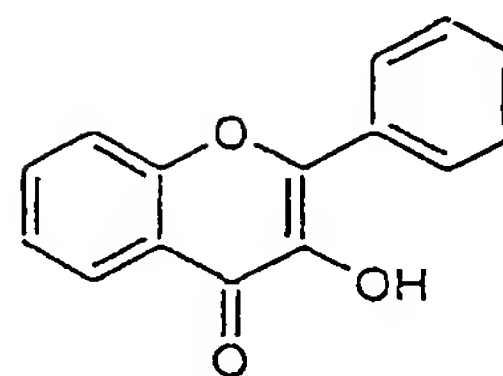
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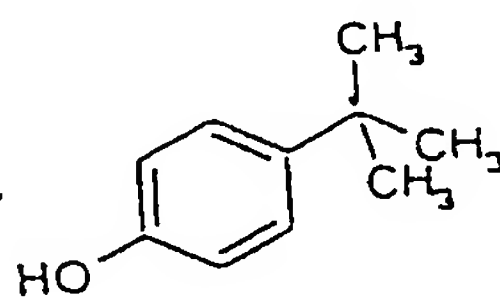
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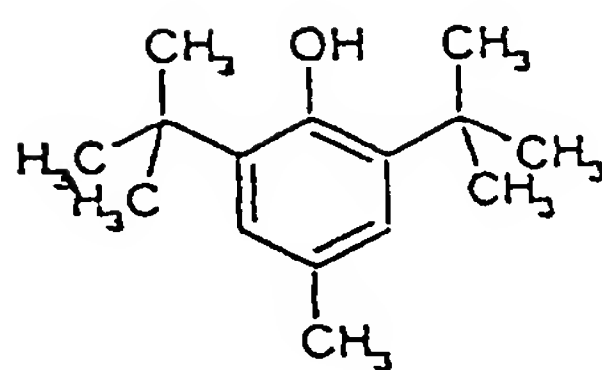
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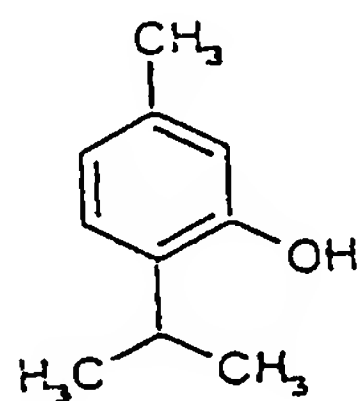
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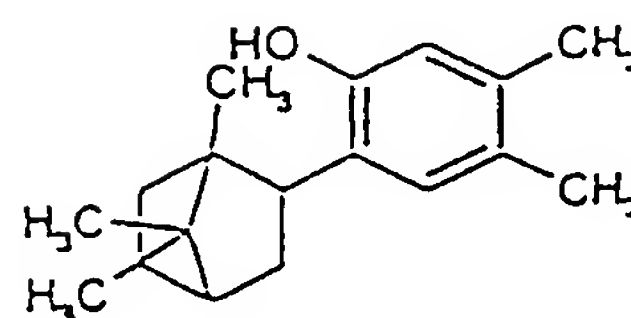
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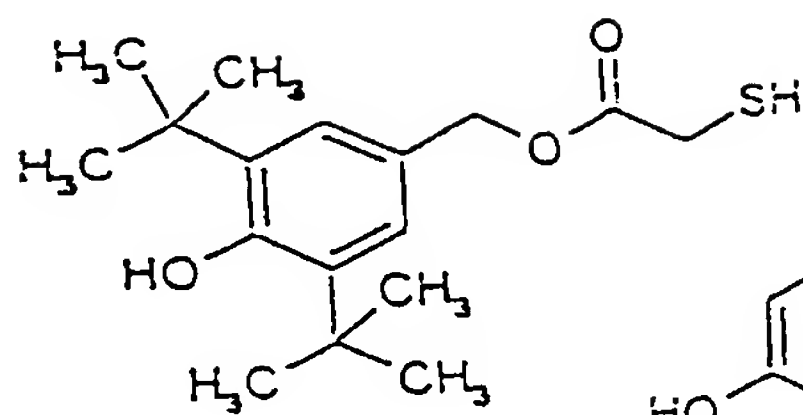
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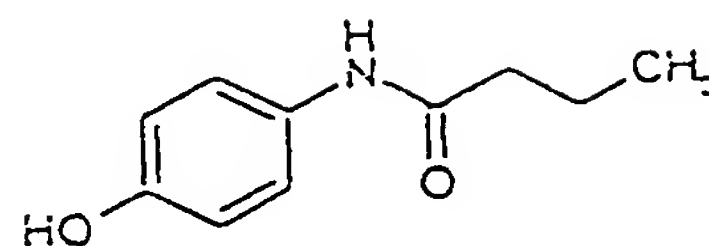
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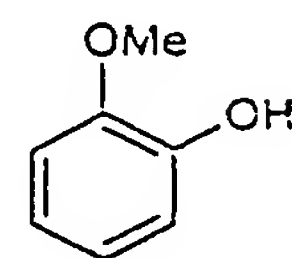
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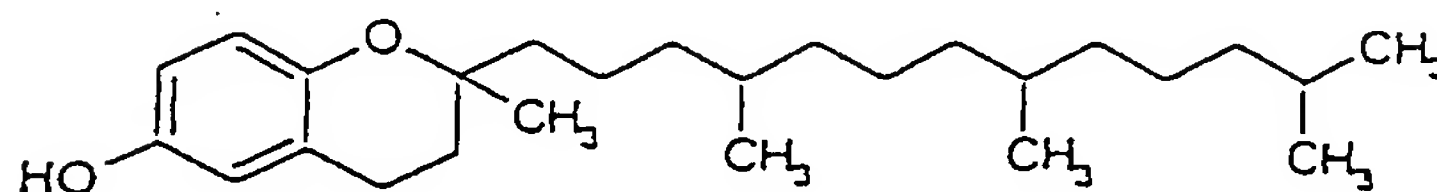
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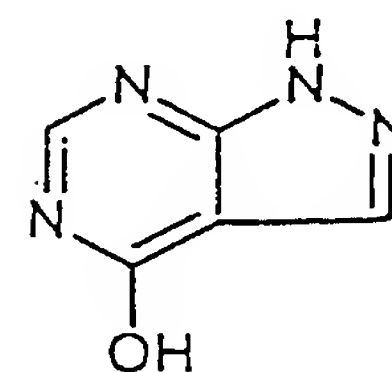
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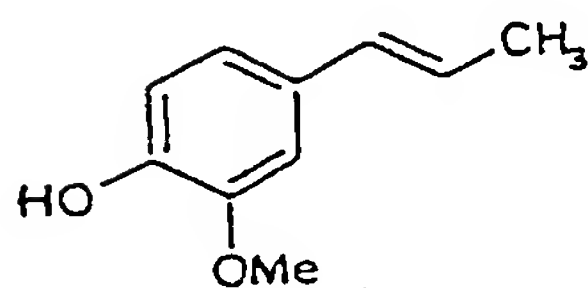
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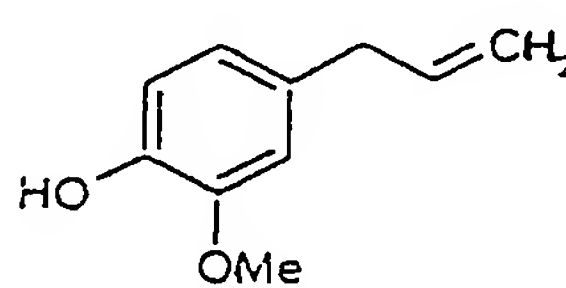
(EXXVII)



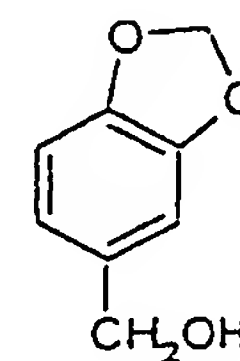
(EXXXI)



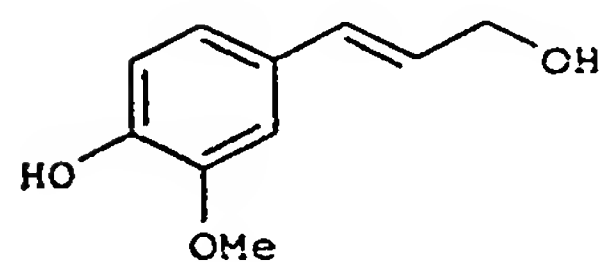
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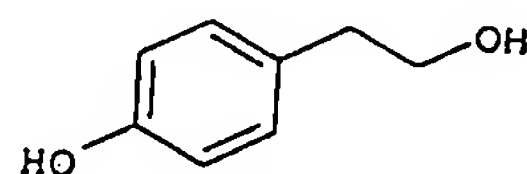
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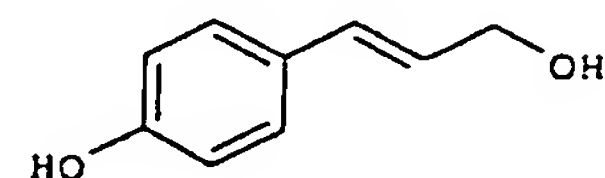
(EXXX)



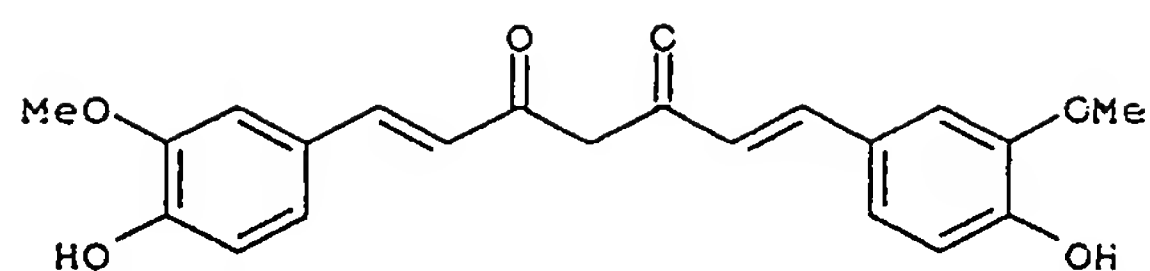
(EXXXII)



(EXXXIII)

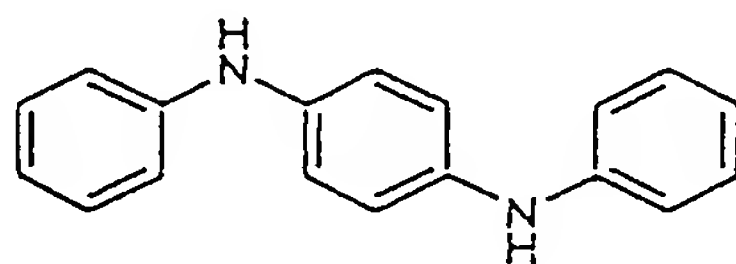


(EXXXIV)

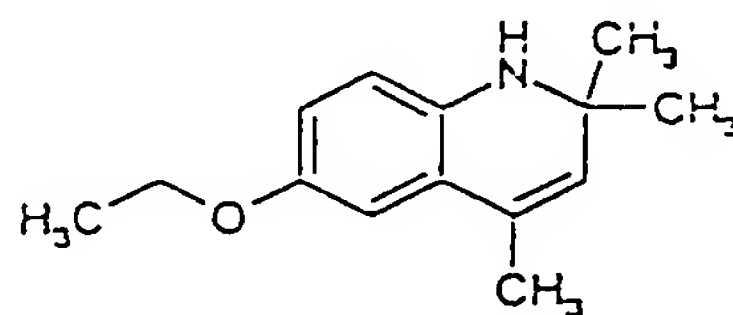


(EXXXV)

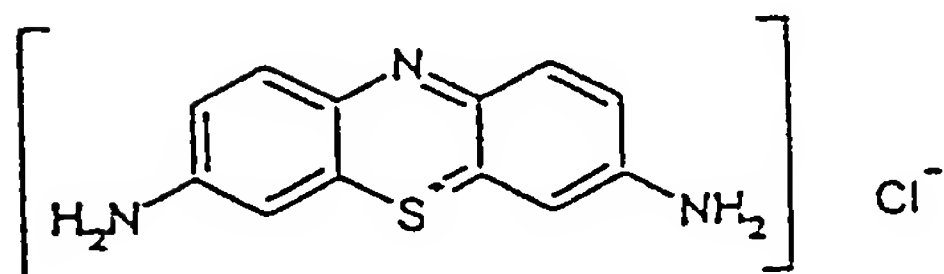
- aromatic and heterocyclic amines, selected from the following: N, N'-diphenyl-p-phenylenediamine (MI), ethoxyquin (MII), thionine (MIII), hydroxyurea (M-IV):



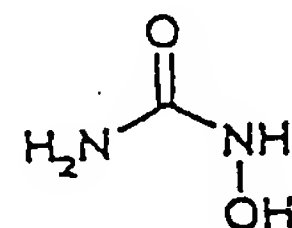
(MI)



(MII)

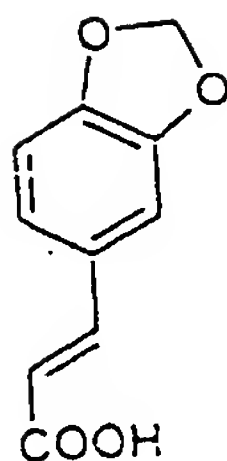


(MIII)

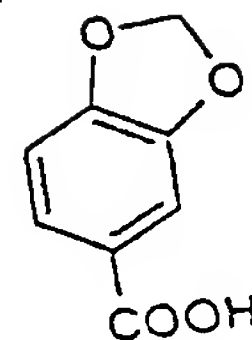


(MIV)

- Compounds containing at least a free acid function, selected from the following: 3,3'-thiodipropionic acid (NI), fumaric acid (NII), dihydroxymaleic acid



(NVII)



(NVIII)

The above mentioned precursors are prepared according to the known methods in the prior art, for example described in "The Merck Index, 12a Ed. (1996), herein incorporated by reference. When available, the corresponding isomers and optical isomers can be used.

Tests 1-3 that are carried out for selecting the precursor drug (hereafter indicated in the tests also as "drug") to be used for the synthesis of the products of the invention are in details the following:

Test 1 (NEM): evaluation of the gastrointestinal damage from oxidative stress induced by free radicals formed following administration of N-ethylmaleimide (NEM) (H.G. Utley, F. Bernheim, P. Hochstein "Effects of sulphhydryl reagents on peroxidation in microsomes" Archiv. Biochem. Biophys. 118, 29-32 1967).

The animals (rats) are distributed in the following groups (no. 10 animals for group):

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, or a physiologic solution when parenterally administered, i.e. by subcutaneous, intraperitoneal, intravenous or intermuscular route),

2° group: treatment: carrier as above defined + NEM,

B) Groups treated with the drug:

group I: treatment: carrier + drug,

gruppo II: treatment: carrier + drug + NEM.

The administration routes are those known for the drug, and can be the oral or subcutaneous, intraperitoneal, intravenous or intramuscular route.

The NEM dose is of 25 mg/kg in physiologic solution (subcutaneous route) and the drug is administered one hour later, in suspension in the carrier, as a single dose which corresponds to the maximum one, or the highest still tolerated by the animals of the group of rats not pretreated with NEM, i.e. the highest administrable dose to said group at which there is no manifest toxicity in the animals, defined as a toxicity that is clearly recognizable for its symptoms. The animals are sacrificed after 24 hours and then one proceeds to the evaluation of the damage to the gastrointestinal mucosa.

The drug meets test 1, i.e. it can be used to prepare the compounds of general formula (I) and (II), when the group of

rats treated with NEM + carrier + drug shows gastrointestinal damages, or in said group the gastrointestinal damages noticed are greater than those shown by the group treated with the carrier alone, or the group treated with carrier + drug, or the group treated with carrier + NEM, even though the drug pharmacotherapeutic efficacy, assayed by using specific tests, is not significantly reduced.

Test 2 (CIP): Protection parameter of endothelial cell against the oxidative stress induced by cumene hydroperoxide (CIP).

Human endothelial cells of the umbilical vein are prepared according to an usual standard procedure. Fresh umbilical veins are filled with a 0.1% by weight collagenase solution and incubated at 37°C for 5 minutes.

Afterwards the veins are perfused with medium M 199 (GIBCO, Grand Island, NY) pH 7.4 further added of other substances, as described in the examples. The cells are collected from the perfusate by centrifugation and harvested in culture flasks T-75, pretreated with human fibronectin. The cells are then harvested in the same medium, further added with 10 ng/ml of bovine hypothalamic growth factor. When the cells of the primary cell culture (i.e. that directly obtained from ex-vivo) form a single layer of confluent cells (about 8,000,000 cells/flask), the culture is stopped and the layers washed and trypsinized. The cellular suspensions are transferred into the

wells of a cell culture plate having 24 wells, half of which is then additioned with the same culture medium containing the drug at a 10^{-4} M concentration, and harvested in a thermostat at 37°C at a constant moisture. Only the cells coming from said first sub-cultures are used for the experiments with cumene hydroperoxide (CIP). The cells are identified as endothelial cells by morphological examination and by their specific immunological reaction towards factor VIII; said cultures did not show any contaminations from myocytes or fibroblasts.

Before starting the test, the cellular culture medium is removed and the cellular layers are carefully washed with a physiologic solution at a temperature of 37°C. The wells of the culture plate are then incubated for one hour with CIP at a 5 mM concentration in the culture medium. The evaluation of cellular damage (apoptosis) is carried out by determining the per cent variation of the DNA fragmentation with respect to the control group (treated with CIP alone), evaluating the fluorescence variation at the wave length of 405-450 nm. 5 replicates for each sample are carried out.

The drug meets the test, i.e. it can be used for preparing the compounds of general formula (I) and (II), when a statistically significant inhibition of apoptosis (cellular damage) induced by CIP with respect to the group treated with CIP alone is not obtained at $p < 0.01$.

Test 3 (L-NAME): evaluation of the endothelial dysfunction

induced by administration of L-NAME (N^w-nitro-L-arginine-methyl ester) J. Clin. Investigation 90, 278-281, 1992.

The endothelial dysfunction is evaluated by determining the damage to the gastrointestinal mucosa, the hepatic damage and blood hypertension induced by administration of L-NAME.

The animals (rats) are divided in groups as herein below shown. The group receiving L-NAME is treated for 4 weeks with said compound dissolved at a concentration of 400 mg/litre in drinking water. The following groups are constituted (No. 10 animals for group):

A) Control groups:

1° group: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, physiologic solution when administered parenterally),

2° group: carrier + L-NAME,

B) Groups administered with the drug:

3° group: carrier + drug,

4° group: carrier + drug + L-NAME.

The administration routes are those known for the drug, and can be the oral or subcutaneous, intraperitoneal, intravenous or intramuscular route. The drug is administered at that dose which results the highest still tolerated by the animals of the group of rats not pretreated with L-NAME, i.e. the highest administrable dose at which there

is no evident toxicity in the animals, i.e. a toxicity recognizable for its symptoms. The drug is administered once a day for 4 weeks.

At the end of the four weeks treatment access to water is prevented and after 24 hours the animals are sacrificed.

One hour before the sacrifice blood-pressure is determined, and a blood pressure increase is taken as an evaluation of the damage to vascular endothelium. The damage to the gastric mucosa is evaluated as illustrated in test 1 (see example F1). The hepatic damage is determined by evaluation of the glutamic-pyruvic transaminase (GPT increase) after sacrifice.

The drug meets test 3, i.e. it can be used for preparing the compounds of general formula (I) and (II), when in the group of rats treated with L-NAME + drug + carrier it is found an higher hepatic damage (GPT) and/or an higher gastric damage and/or an higher cardiovascular (blood-pressure) damage in comparison to that of the group treated with the carrier alone, or of the group treated with carrier + drug, or of the group treated with carrier + L-NAME; even if the drug pharmacotherapeutic efficacy, assayed by specific tests, is not significantly reduced.

Under the conditions indicated in the above described in vivo tests 1 and 3 the therapeutic index of the drug is reduced since the usual doses at which the drug can be effective are no

longer tolerated.

Test 4 is a colorimetric test which affords to establish whether the precursor of B or B₁ (precursor of the X₂ or X_{2a} of the formulas (I) and (II) respectively), inhibits the production of radicals from DPPH (2,2-diphenyl-1-picryl-hydrazyl) (M.S. Nenseter et Al., Atheroscler. Thromb. 15, 1338-1344, 1995). 100 µM solutions in methanol of the tested substances are prepared, and an aliquot of each of said solutions is added to a DPPH solution in methanol 0.1 M. After having stored the solutions at room temperature away from light for 30 minutes, their absorbances are read at the wave length of 517 nm, together with that of the corresponding DPPH solution at the same concentration. The absorbance decrease with respect to that of the solution of DPPH at the same concentration of the test solutions is determined. The effectiveness of the tested compound in inhibiting formation of radicals by DPPH is expressed by the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the test compound together with DPPH and of the solution containing only DPPH.

The B or B₁ precursor satisfies test 4 if their effectiveness in inhibiting radical production as above defined, is equal to or higher than 50% at the indicated concentration (10⁻⁴ M).

Unexpectedly the products of the invention of the formulas (I) and (II) in oxidative stress conditions have an improved therapeutic index compared with the precursor drugs.

For illustrative purposes the above mentioned tests are referred to the following compounds (see the Examples):

Test 1: precursor drug: indomethacin

- Maximum administrable dose to rats: 7.5 mg/Kg p.o. By administering a higher dose a toxicity is manifested, characterized by enteropathy, tremor, sedation until death (within 24 hours).
- The group of rats treated with NEM + indomethacin at the above mentioned dose shows gastrointestinal damages.

Since indomethacin in the groups treated with NEM causes gastrointestinal damages, it meets test 1. Indomethacin can therefore be used as a drug for preparing the compounds (I) and (II) of the present invention.

Test 2: precursor drugs: indomethacin, paracetamol and mesalamine

Indomethacin and paracetamol meet test 2 since the cellular damage (apoptosis) inhibition induced by CIP is not significantly different with respect to that of the controls.

Therefore the above drugs can be used as drugs for preparing the compounds (I) and (II) of the present invention.

On the contrary mesalamine does not meet test 2, since it inhibits the apoptosis induced by CIP. Therefore mesalamine

according to test 2 could not be used as a precursor to prepare the compounds (I) and (II) of the present invention. It has been however found that mesalamine submitted to test 1 causes gastrointestinal damages.

Thus also mesalamine can be used as a precursor for preparing the compounds (I) and (II) of the present invention. Test 3 (L-NAME) precursor drugs: paracetamol, simvastatin, omeprazole

Paracetamol and simvastatin meet test 3 since they cause gastric and hepatic damages greater than those induced both by L-NAME + carrier and by the drug + carrier.

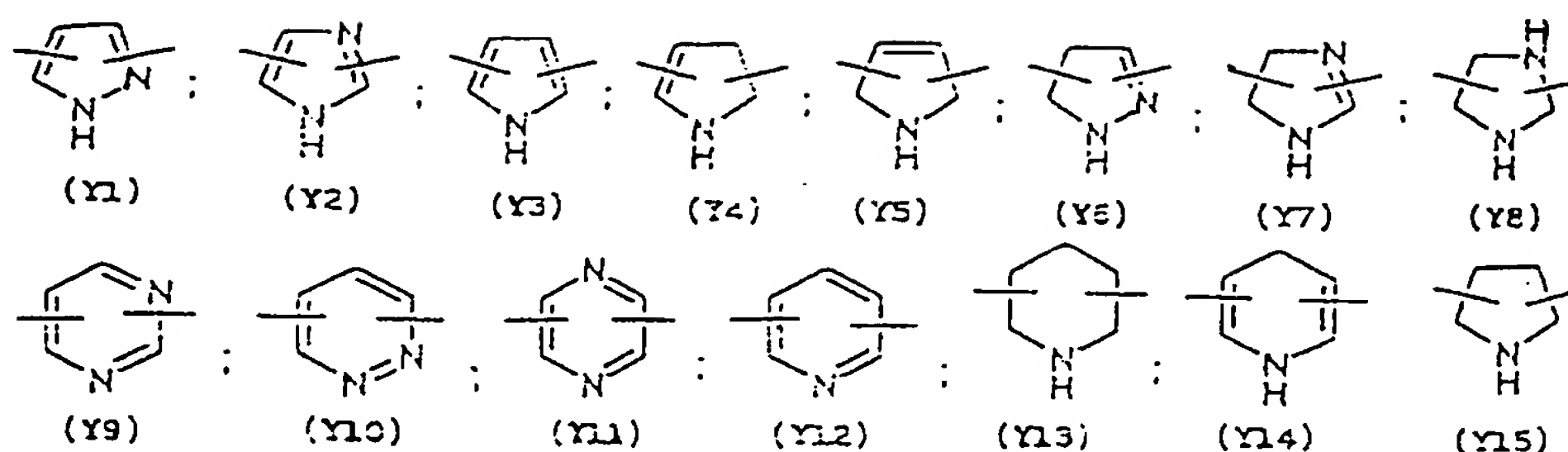
Therefore they can be used as precursors to prepare the compounds (I) and (II) of the present invention.

On the contrary it has been found that omeprazole neither causes gastric nor hepatic damages, nor influences blood-pressure. According to test 3 omeprazole could not be used as a precursor for preparing the compounds (I) and (II) of the present invention.

Test 4 (test for the precursor of B and B₁ used as bivalent linking bridge): precursor N-acetylcysteine

N-acetylcysteine inhibits of 100% the production of radicals induced by DPPH, therefore it meets test 4. Therefore it can be used as precursor of B or B₁.

In formula (III) Y³ is preferably selected from the following:



The most preferred of Y^2 is Y12 (pyridyl) substituted in positions 2 and 6. The bonds can also be in asymmetric position, for example Y12 (pyridyl) can be substituted also in position 2 and 3; Y1 (pyrazol) may be 3,5-disubstituted.

The compounds according to the present invention of formula (I) and (II) can be transformed into the corresponding salts. For example one route to form the salts is the following: when in the molecule one nitrogen atom sufficiently basic to be salified, in organic solvent such as for example acetonitrile, tetrahydrofuran, is present, it is reacted with an equimolecular amount of the corresponding organic or inorganic acid. To form the salt, preferably in the formula of the invention compounds Y or Y' of formula (III) is present.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acids.

Examples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acids.

The derivatives according to the invention can be used in the therapeutic indications of the precursor drug, allowing to obtain the advantages exemplified hereinafter for some groups

of these drugs:

- Anti-inflammatory drugs NSAIDs: the invention compounds result very well tolerated and effective, even when the organism is debilitated and is under conditions of oxidative stress. Said drugs can be used also in those pathologies wherein inflammation plays a significant pathogenetic role, such as for instance, but not limited to, in cancer, asthma, miocardic infarction.
- Adrenergic blockers, of α - or β -blocker type: the action spectrum of the compounds of formula (I) and (II) results wider than that of the starting drugs; to a direct action on the smooth musculature the inhibition of the nervous beta-adrenergic signals governing the contraction of the hematic vessels is associated. The side effects (dyspnoea, bronchoconstriction) affecting the respiratory apparatus are lower.
- Antithrombotic drugs: the antiplatelet activity is potentiated and in the case of the aspirin derivatives the gastric tolerability is improved.
- Bronchodilators and drugs active on the cholinergic system: the side effects affecting the cardio-vascular apparatus (tachycardia, hypertension) result lowered.
- Expectorants and mucolytic drugs: the gastrointestinal tolerability results improved.
- Diphosphonates: the toxicity relating to the gastrointe-

stinal tract is drastically lowered.

- Phosphodiesterase (PDE) (bronchodilators) inhibitors: the therapeutic efficacy is improved, the dosage being equal; it is therefore possible, using the compounds of the invention to administer a lower dose of the drug and reduce the side effects.
- Anti leukotrienic drugs: better efficacy.
- ACE inhibitors: better therapeutic efficacy and lower side effects (dyspnoea, cough) affecting the respiratory apparatus.
- Antidiabetic drugs (insulin-sensitizing and hypoglycaemizing) antibiotic, antiviral, antitumoral, anticolitic drugs, drugs for the dementia therapy: better efficacy and/or tolerability.

The drugs which can be used as precursors in formulas (I) and (II) of the compounds of the invention are all those meeting at least one of the above mentioned tests 1, 2, 3. Examples of precursor drugs which can be used are the following:

For anti-inflammatory/analgesic drugs, the following can for example be mentioned:

anti-inflammatory drugs: aceclofenac, acemetacin, acetylsalicylic acid, 5-amino-acetylsalicylic acid, alclofenac, alminoprofen, amfenac, bendazac, bermoprofen, α -bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen,

cinmetacin, clidanac, clopirac, diclofenac sodium, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, oxaceprol, oxaprozin, oxyphenbutazone, parsalmide, perisoxal, phenyl acetylsalicylate, olsalazine, pyrazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicylamide O-acetic acid, salicylsulphuric acid, salsalate, sulindac, suprofen, suxibuzone, tenoxicam, tiaprofenic acid, tiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepirac, tomoxiprol;

analgesic drugs: acetaminophen, acetaminosalol, aminochlorthenoxazin, acetylsalicylic 2-amino-4-picoline acid, acetylsalicylsalicylic acid, anileridine, benoxaprofen benzylmorphine, 5-bromosalicylic acetate acid, bucetin, buprenorphine, butorphanol, capsaicine, cinchophen, ciramadol, clometacin, clonixin, codeine, desomorphine, dezocine, dihydrocodeine, dihydromorphine, dimepheptanol, dipyroacetyl, eptazocine, ethoxazene, ethylmorphine, eugenol, floctafenine, fosfosal, glafenine, hydrocodone, hydromorphone, hydroxypethidine, ibu-

fenac, p-lactophenetide, levorphanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nicomorphine, norlevorphanol, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, phenocoll, phenoperidine, phenylbutazone, phenylsalicylate, phenylramidol, salicin, salicylamide, tiorphan, tramadol, diacerein, actarit;

for respiratory and urogenital apparatus drugs (bronchodilators and drugs active on the cholinergic system, expectorants/mucolytics, antiasthmatic/antiallergic antihistaminic drugs), the following can be mentioned:

broncodilators and drugs active on the cholinergic system :
acefylline, albuterol, bambuterol, bamifylline, bevonium methyl sulphate, bitolterol, carbuterol, clenbuterol, chlorprenaline, dioxethedrine, difylline, ephedrine, epinephrine, eprozinol, etafredine, ethylnorepinephrine, etofylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium bromide, isoetharine, isoprotenerol, mabuterol, metaproterenol, oxybutynin, oxitropium bromide, pirbuterol, procaterol, protokylol, proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, 1-teobromineacetic acid, tiotropium bromide, tretoquinol, tulobuterol, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetra hydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: ambroxol, bromhexine, domiodol, erdosteine, guaiacol, guaifenesin, iodinated glycerol, leto-

steine, mesna, sobrerol, stepronin, terpin, tiopronin;

antiasthmatic/antiallergic antihistaminic drugs: acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam, chromoglycate, chromolyn, epinastine, fexofenadine, formoterol, histamine, hydroxyzine, levocabastine, lodoxamide, mabuterol, metron s, montelukast, nedocromil, repirinast, seratrodist, suplatast tosylate, terfenadine, tiaramide, urushiol, bromhexine;

for cardiovascular drugs (ACE-inhibitors, beta-blockers, antithrombotic and vasodilator drugs, antidiabetic and hypoglycemic drugs), the following can be mentioned:

ACE-inhibitors: alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, losartan, moveltipril, naphthopidil, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, urapidil;

beta-blockers: acebutolol, alprenolol, amosulalol, arotinolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, dilevalol, epanolol, esmolol, indenolol, labetalol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipridalol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol;

antithrombotic and vasoactive drugs: acetorphan, acetylsa-

licylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betahistine, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, dalteparin, dipyridamole, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, heparin, lamifiban, midrodine, nadroparin, nicotiny alcohol, nylidrin, ozagrel, perhexiline, phenylpropanolamine, prenylamine, papaveroline, reviparin sodium salt, ridogrel, suloctidil, tinofedrine, tinzaparin, triflusal, xanthinol niacinate;

antidiabetic drugs: acarbose, carbutamide, glibornuride glybuthiazol(e), miglitol, repaglinide, troglitazone, 1-butyl-3-metanyl-urea, tolrestat, nicotinamide;

for antitumor drugs, the following can be mentioned: ancitabine, anthramycin, azacitidine, azaserine, 6-azauridine, bicalutamide, carubicin, carzinophilin, chlorambucil, chlorozotocin, cytarabine, daunorubicin, defosfamide, demecolcine, denopterin, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicin, droloxifene, edatrexate, eflornithine, enocitabine, epirubicin, epitiostanol, etanidazole, etoposide, fenretinide, fludarabine, fluorouracil, gemcitabine, hexestrol, idarubicin, lonidamine, mannomustine, melphalan, menogaril, 6-mercaptopurine, methotrexate, mitobronitol, mitolactol, mitomycins, mitoxantrone, mopidamol, mycophenolic acid, ninopterin, nogalamycin, paclitaxel, pentostatin, pirarubicin, piritrexim, plicamycin, podophyllic acid, porfimer

sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, thiamiprine, thioguanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicin;

for antiulcer drugs the following can be mentioned: ϵ -acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecbet, enprostil, esaprazole, irsogladine, misoprostol, omeprazole, ornoprostil, pantoprazole, plaunotol, rioprostil, rosaprostol, rotraxate, sofalcone, trimoprostil;

among anti-hyperlipidemic drugs (statines) the following can be mentioned: atorvastatin, cilastatin, dermostatin, fluvastatin, lovastatin, mevastatin, nystatin, pentostatin, pepstatin, privastatin sodium, simvastatin;

among antibiotic/antiviral drugs the following can be mentioned:

antibiotics: amdinocillin, amoxicillin, ampicillin, apalcillin, apicycline, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoylpas, benzyl penicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin,

cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephaetrile sodium, cephalixin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cepnapirin sodium, cephradine, chloramphenicol, chlortetracycline, cinoxacin, clavulanic acid, clometocillin, cloxacillin, cyclacillin, cycloserine, demeclocycline, dicloxacillin, epicillin, fenbecillin, flomoxef, floxacillin, hetacillin, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, meclocycline, meropenem, metampicillin, methacycline, methicillin sodium, mezlocillin, minocycline, moxalactam, mupirocin, myxin, negamycin, novobiocin, oxacillin, panipenem, penicillin G potassium salt, penicillin N, penicillin O, penicillin V, phenethicillin potassium salt, pipacycline, piperacillin, pirlimycin, porfirimycin, propcillin, quinacillin, ritipenem, rolitetracycline, sancycline, sedecamycin, spectinomycin, sulbactam, sulbenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidin, azithromycin, clarithromycin, dirithromycin, enviomycin, erythromycin, josamycin, midecamycin, miokamycin, oleandomycin, rifabutin, rifamide, rifamycin, rifaximin, rokitamycin, spiramycin, troleandomycin, viomycin, virginiamycin;

amikacin, apramycin, arbekacin, dibekacin, dihydrostreptomycin, fortimicins, gentamicin, micronomicin, neomycin, netilmicin,

paromomycin, ribostamycin, sisomicin, spectinomycin,
streptomycin, tobramycin, trospectomycin;
bacampicillin, cefcapene pivoxil, cefpodoxime proxetil,
panipenem, pivampicillin, pivcefalexin, sultamicillin,
talampicillin;
carbomycin, clindamycin, lincomycin, mikamycin, rosaramicin,
ciprofloxacin, clinafloxacin, difloxacin, enoxacin,
enrofloxacin, fleroxacin, flumequine, grepafloxacin,
lomefloxacin, nadifloxacin, nalidixic acid, norfloxacin,
ofloxacin, pazufloxacin, pefloxacin, pipemidic acid, piromidic
acid, rufloxacin, sparfloxacin, tosufloxacin, trovafloxacin,
clomocycline, guamecycline, oxytetracycline, nifurpirinol,
nifurprazine; p-aminosalicylic acid, p-aminosalicylic acid
hydrazide, clofazimine, deoxydihydrostreptomycin, ethambutol,
glyconiazide, isoniazid, opiniazide, phenyl aminosalicylate,
rifampin, rifapentine, salinazid, 4-4'-sulfynyldianiline,
Acediasulfone, dapson, succisulfone, p-sulfanilylbenzylamine,
thiazolsulfone, acetyl sulfamethoxypyrazine, mafenide, 4'-
(methylsulfamoyl)sulfanilanilide, salazosulfadimidine,
sulfabenzamide, sulfacetamide, sulfachlorpyridazine,
sulfachrysoidine, sulfacytine, sulfadiazine, sulfadicramide,
sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine,
sulfaguanole, sulfalene, sulfamerazine, sulfameter,
sulfamethazine, sulfamethizole, sulfamethomidine,
sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole,

sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 2-p-sulfanilylanilinoethanol, N⁴-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfisomidine, sulfisoxazole, 4-sulfanilamido salicylic acid; negamycin, carumonan, cloxyquin, nitroxoline, arginine, metronidazole;

antiviral drugs: aciclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, flouxuridine, ganciclovir, idoxuridine, indanavir, kethoxal, lamivudine, MADU, penciclovir, podophyllotoxin, ribavirin, rimantadine, saquinavir, sorivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine;

among inhibitors of the bone resorption (diphosphonates) the following can be mentioned: alendronic acid, butedronic acid, etidronic acid, oxidronic acid, pamidronic acid, risedronic acid;

among antidementia drugs the following can be mentioned:

amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

The preferred substances are the following:

among anti-inflammatories: acetylsalicylic acid, 5-aminoacetylsalicylic acid, carprofen, diclofenac sodium, diflunisal, etodolac, flufenamic acid, flunixin, flurbiprofen,

ibuprofen, indomethacin, indoprofen, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, naproxen, niflumic acid, olsalazine, piroxicam, salsalate, sulindac, suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, tolmetin, zomepirac, tomoxiprol;

among analgesic drugs: acetaminophen, acetylsalicylsalicylic acid, benoxaprofen, buprenorphine, butorphanol, capsaicin, diacerein, dihydrocodeine, ethylmorphine, eugenol, phenylbutazone, meptazinol, morphine, nalbuphine, pentazocine, thiorphan, tramadol, actarit;

among respiratory and urogenital apparatus drugs: (bronchodilators, drugs active on the cholinergic system, expectorants / mucolytics, antiasthmatics/antiallergic antihistaminic drugs):

bronchodilators and drugs active on the cholinergic system: albuterol, carbuterol, clenbuterol, difhylline, etofylline, fenoterol, ipratropium bromide, metaproterenol, oxybutynin, pirbuterol, salmeterol, terbutaline, tiotropium bromide, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetrahydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: ambroxol, bromexine, guaiaicol, sobrerol;

antiasthmatic/antiallergic antihistaminic drugs: cetirizine, chromoglycate, histamine, levocabastine, lodoxamide, montelukast, terfenadine, bromexine;

among cardiovascular drugs:

ACE-inhibitors: captopril, enalapril, lisinopril, losartan, ramipril;

Beta blockers: alprenolol, atenolol, bupranolol, labetalol, metipranolol, metoprolol, pindolol, propranolol, timolol;

antithrombotic and vasoactive drugs: acetylsalicylic acid, acetorphan, argatroban, clopidogrel, dalteparin, dipyridamole, enoxaparin, heparin, iloprost, midodrine, ozagrel, phenylpropanolamine, trifusal;

antidiabetic drugs: tolrestat, nicotinamide;

among antitumor drugs: anthracyclin, daunorubicin, doxorubicin, epirubicin, fluorouracyl, methotrexate, vinblastine;

among antiulcer drugs: cimetidine, omeprazole, pantoprazole;

among antihyperlipidemic drugs: lovastatin, pravastatin sodium, simvastatin;

among antibiotic/antiviral drugs:

antibiotic drugs: amoxicillin, ampicillin, aztreonam, biapenem, carbenecillin, cefaclor, cefadroxil, cefamandole, cefatrizine, cefoxitin, clavulanic acid, dicloxacillin, imipenem, meclocycline, methacycline, moxalactam, panipenem, sulbactam, azithromycin, erythromycin, josamycin, miokamycin, rifabutine, rifamide, rifamycin, gentamicin, paromomycin, sisomicin, bacampicillin, carbomycin, clindamycin, ciprofloxacin, clinafloxacin, difloxacin, enrofloxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pipemidic acid,

apicycline, clomocycline, oxytetracycline, nifurpirinol, nifurprazine, isoniazid, rifampin, rifapentine, dapsone, thiazolsulfone, sulfamethoxazole, sulfamoxole, metronidazole, arginine;

antiviral drugs: aciclovir, famciclovir, ganciclovir, penciclovir, ribavirin, vidarabine, zidovudine;

among inhibitors of the bone reabsorption: alendronic acid, etidronic acid, pamidronic acid;

among antidemence drugs: oxiracetam, tacrine, velnacrine.

The above mentioned substances, precursor drugs, are prepared according to the methods known in the prior art. See for example in "The Merck Index, 12a Ed. (1996), herein incorporated by reference. When available, the corresponding isomers, comprising optical isomers, can be used.

Tomoxiprol is obtained according to the method described in EP 12,866.

The compounds of formula (I) or (II) are prepared with synthesis methods mentioned below.

The choice of the reactions for each method depends on the reactive groups present in the precursor drug molecule, in the precursor compound of B or B₁, which can be, as above mentioned, bivalent or monovalent, and in the precursor compound of C.

The reactions are carried out with methods well known in the prior art, which allow to obtain bonds among the precursor

drug, the precursor drug of E or B₁ and the precursor compound of C as above defined.

When the reactive function of the precursor drug (for example -COOH, -OH) is involved in a covalent bond, for example of ester, amide, ether type, said function can be restored with the methods well known in the prior art.

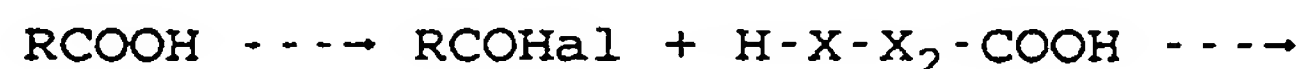
Some synthesis schemes for obtaining the compounds of the invention are reported hereinafter:

A) Synthesis of the compounds of formula (I).

1. Synthesis of the compound obtained by reaction between the precursor drug and the compound precursor of B.

1a. When the drug has general formula R-COOH and the functional group of the precursor compound of B which binds itself to the drug carboxylic function has the formula XZ, X being as above defined and Z = H, the reactions which take place depend on the nature of the second reactive group present in the precursor compound of B.

1a.1 When the second reactive group present in the precursor compound of B is a carboxylic group, the synthesis general scheme expects the initial formation of the halide of the R-COHal acid (Hal = Cl, Br) and the subsequent reaction with the HX group of the precursor compound of B:



X₂, T₁, T₃ being as above defined.

When in the two reaction compounds other functional groups COOH and/or HX are present, they must be protected before the reaction according to the methods known in the art; for example as described in the volume by Th. W. Greene: "Protective groups in organic synthesis", Harvard University Press, 1980.

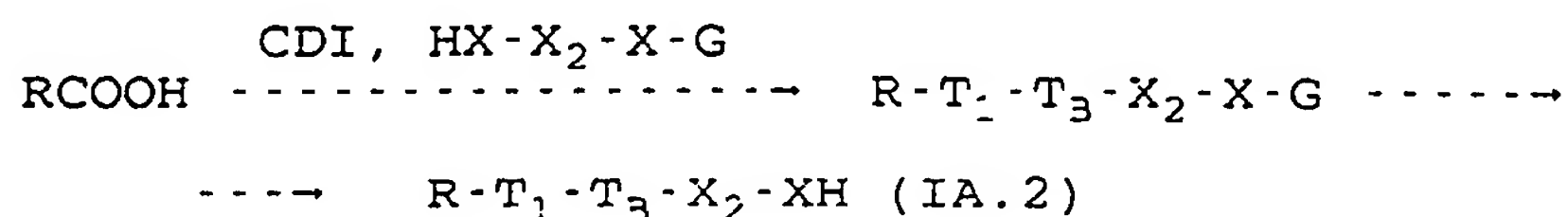
The RCOHal acylhalide is prepared according to the methods known in the prior art, for example by thionyl or oxalyl chloride, P^{III} or P^V halides in inert solvents under the reaction conditions, such as for example toluene, chloroform, DMF, etc.

Specifically, if the HX group of the precursor compound of B is NH_2 , or OH or SH, the precursor drug of formula R-COOH is first converted into the corresponding acyl halide RCOHal, as above mentioned, and then reacted with the HX group of the precursor compound of B in the presence of an organic base, such as triethylamine, pyridine, etc. using an inert solvent in the reaction conditions such as toluene, tetrahydrofuran, etc. at a temperature in the range $0^{\circ}C-25^{\circ}C$.

Alternatively to the previous synthesis, the precursor drug of formula R-COOH can be treated with an agent activating the carboxyl group selected from N,N'-carbonyldiimidazol (CDI), N-hydroxybenzotriazol and dicyclohexylcarbodiimide in solvent such as for example DMF, THF, chlo-

roform etc. at a temperature in the range -5°C - 50°C and the obtained compound reacted in situ with the reactive function of the precursor compound of B for obtaining the compound of formula (IA.1).

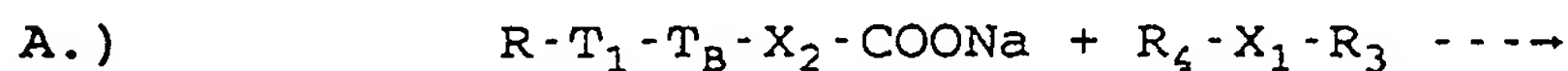
1a.2 When the precursor compound of B contains two functional groups XZ, equal to or different from each other, X being as above defined and $Z = \text{H}$, the precursor drug having formula R-COOH is first treated with an agent activating the carboxyl group, as above described in 1a.1, and then with the precursor compound of B, after having protected one of the two reactive HX groups, for example with acetyl or ter-butyloxycarbonyl, restoring the initial function at the synthesis end. The scheme is the following:

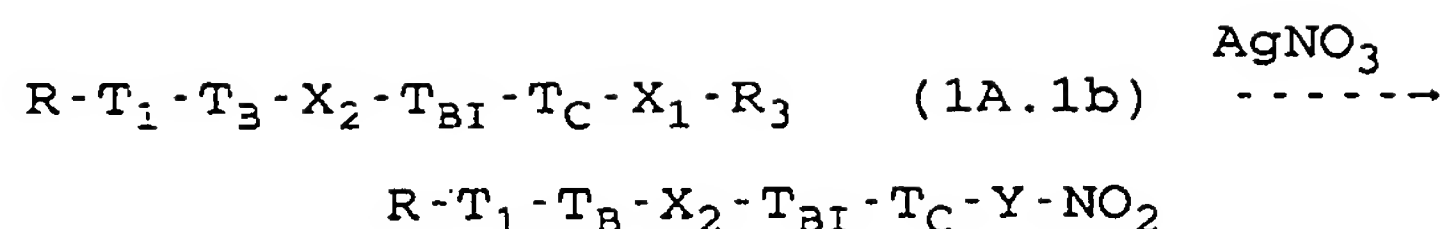


wherein X, T_1 , T_3 , X_2 are as above defined and G is a protective group of the HX function.

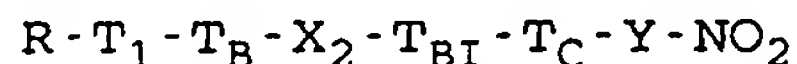
2. Nitroxyderivative synthesis.

2a.1 When the compound obtained at the end of the previous step 1a. has formula (IA.1), the acid can be converted into the corresponding sodic salt and then one can follow the known prior art methods for preparing the final compound, for example according to one of the following synthesis schemes:

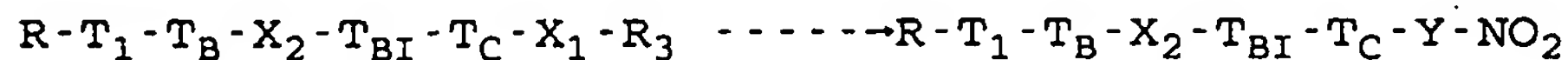
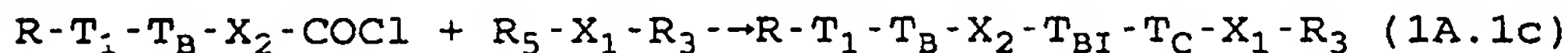




wherein T_1 , T_3 , X_2 , T_{BI} , T_C are as above defined, R_4 is selected from Cl, Br, Y is as above defined, X_1 is the Y radical free from the oxygen atom, R_3 is Cl, Br, Iodine, OH. If $R_3 = \text{OH}$ the compound of formula (1A.1b) is subjected to halogenation, for example with PBr_3 , PCl_5 , SOCl_2 , $\text{PPh}_3 + \text{I}_2$, and then reacted with AgNO_3 in organic solvent such as acetonitrile, tetrahydrofuran. If R_3 is Cl, Br, Iodine, the compound of formula (1A.1b) is directly reacted with AgNO_3 as above mentioned.



C.)



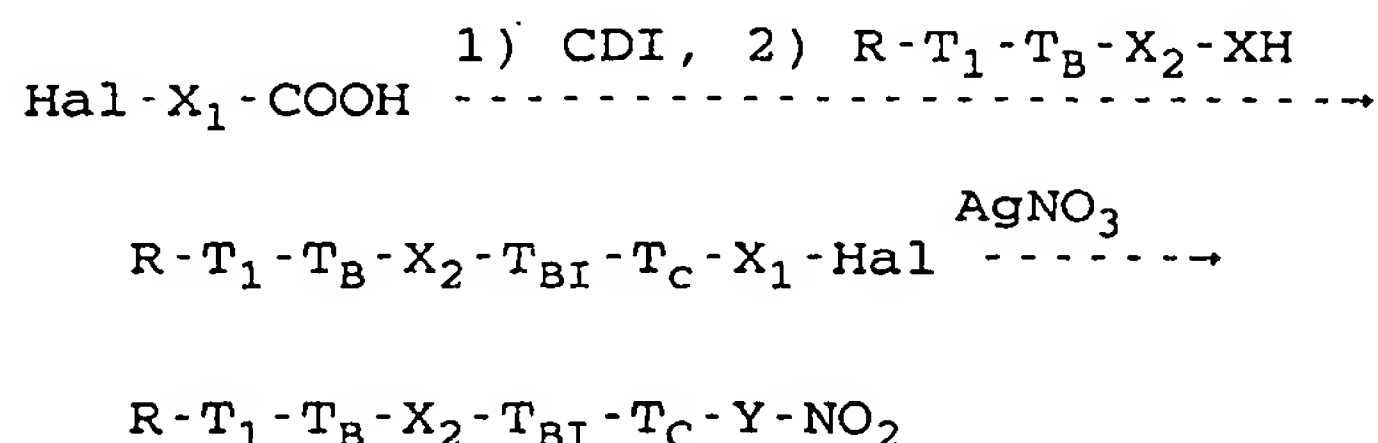
wherein $R_5 = \text{OH}$ or $\text{NHR}_{1\text{C}}$, $R_{1\text{C}}$, R_3 and the other symbols being as above defined.

The above shown reactions are well known in the prior art. See for example the patent applications in the name of the Applicant WO 94/12463, WO 95/09831 and WO 95/30641.

When X_1 is a linear C_4 alkyl, the corresponding acid $\text{R-T}_1\text{-T}_3\text{-X}_2\text{-COOH}$ is reacted with triphenylphosphine in the

presence of an halogenating agent such as CBr_4 or N-bromosuccinimide in tetrahydrofuran obtaining the compound (1A.1c) wherein $\text{R}_3 = \text{Br}$.

2a.2 When the compound obtained at the end of the previous step 1a has formula (IA.2), the corresponding nitroxyderivative is obtained by treating an halogen-carboxylic acid of formula $\text{Hal-X}_1\text{-COOH}$, X_1 being as above defined, first with an agent activating the carboxyl group as described in 1A.1, and then with the compound of formula (IA.2), obtaining an halogen derivative, which is isolated and then dissolved in organic solvent, (ref. paragraph 2a.1), and treated with silver nitrate. The global reaction scheme is the following:

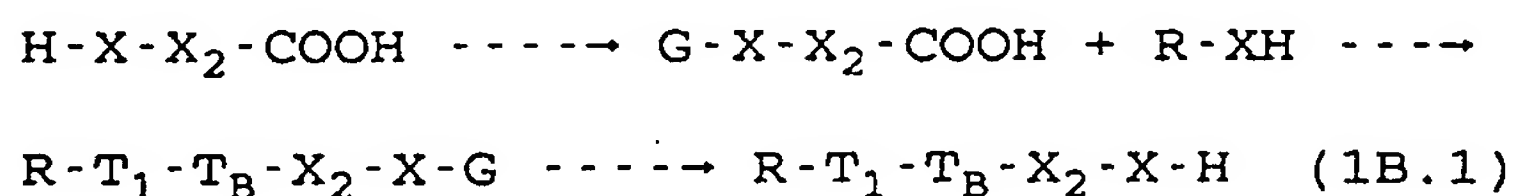


wherein T_1 , T_B , X_2 , T_{BI} , T_C , Y are as above defined.

Alternatively, the halide $\text{Hal-X}_1\text{-COCl}$ can be used, wherein Hal is preferably bromine, which is let react with the compound of formula (IA.2).

1b. When the drug precursor has the reactive function HX , wherein X is as above defined, instead of a carboxylic group, the two functional groups present on the precursor compound of B can be the following:

1b.1 A carboxylic group, which reacts with the HX function of the drug precursor, and a HX group, the latter reactive group of the precursor compound of B being equal to or different from the functional group of the drug precursor. The formula of the precursor compound of B is of the H-X-X₂-COOH type, wherein X and X₂ are as above defined. The H-X- function of the precursor compound of B is protected according to the known prior art methods and the carboxyl group is reacted, as above mentioned, according to the following scheme:



At the end of the reaction the HX function of the precursor compound of B is restored.

1b.2 When the precursor compound of B contains two carboxylic groups, it is treated with an equimolar amount of an agent activating the carboxyl group under the conditions previously described in 1a.1, and then reacted with the reactive HX function of the drug precursor molecule. Possible other reactive functions of HX type present in the two compounds must be protected as previously mentioned. Lastly a compound of formula R-T₁-T_B-X₂-COOH (1B.2) is obtained.

2b. Nitroxyderivative synthesis.

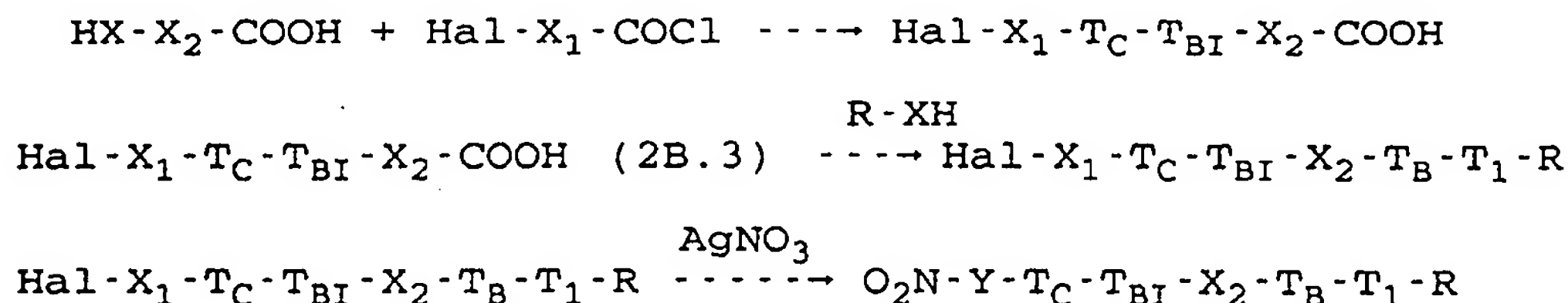
2b.1 To obtain the final nitroxyderivative starting from the

compound of formula $R-T_A-T_B-X_2-X-H$ (1B.1), obtained at the end of the synthesis described in 1b.1, the (1B.1) compound is reacted with an halogenacid of formula $Hal-X_1-COOH$ which has been treated as previously described in paragraph 1a.1, or with the corresponding halogenacid chloride. The resulting compound is dissolved in organic solvent, for example acetonitrile or tetrahydrofuran and reacted with silver nitrate.

2b.2 To obtain the final nitroxyderivative starting from the compound of formula $R-T_A-T_B-X_2-COOH$ (1B.2), obtained at the end of the synthesis described in 1b.2, the acid is transformed into the corresponding sodic salt, it is reacted with a $R_4-X_1-R_3$ compound, previously defined in the reaction A. scheme of paragraph 2a.1, obtaining according to the same process therein mentioned the final nitroxyderivative. Alternatively, when X_1 is a linear C_4 alkyl, the acid (1B.2) is reacted with triphenyl-phosphine in the presence of an halogenating agent such as CBr_4 or N-bromosuccinimide in tetrahydrofuran and the resulting compound dissolved in organic solvent for example acetonitrile, tetrahydrofuran, is reacted with silver nitrate.

2b.3 Alternatively to the synthesis process according to 1b.1 and 2b.1, it is possible to react in a first step the HX -function of the precursor compound of B $HX-X_2-COOH$ with

the acyl chloride of an halogenacid of formula Hal-X₁-CO-Cl, wherein Hal is preferably Br, and subsequently the carboxylic function of the so obtained compound, with the drug precursor R-HX. In the third and last step the -Hal group is substituted with -ONO₂ according to the process described in 2b.1. The reaction scheme is the following:



wherein T_C, T_{BI}, T_B, T₁, X₂, X₁, Y are as above defined.

In the previous scheme the nitration can alternatively be carried out on the acid compound of formula (2B.3).

B) Synthesis of compounds of formula (II).

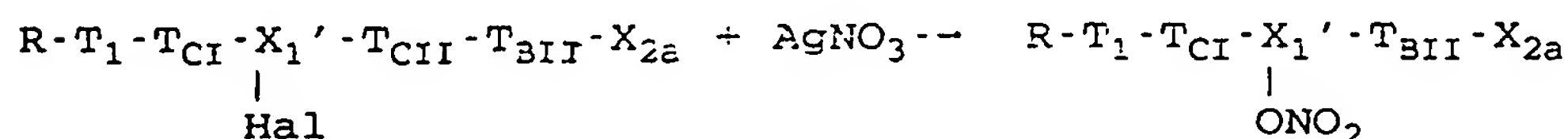
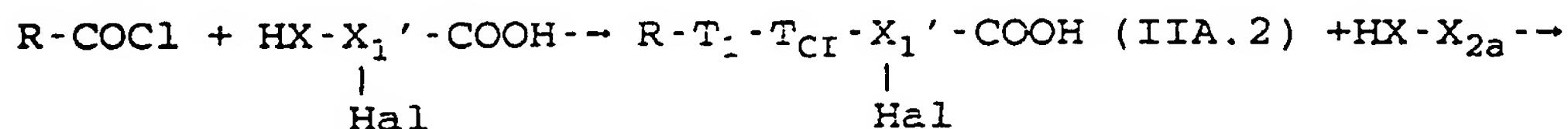
1a. When the drug precursor is of formula R-COOH and the precursor compound of B₁ contains only one functional reactive group of formula XH, X being as above defined, R-COOH is initially converted into the corresponding acyl-halide, or treated with an agent activating the carboxyl group as described in 1a.1, and then reacted with the HX function of an halogen-acid compound, said function being equal to or different from that present on the precursor compound of B₁, said halogen-acid having the formula:



wherein X₁' is Y' as above defined without the oxygen atom

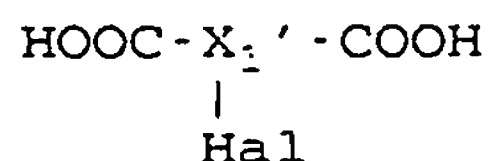
through which the $-\text{NO}_2$ group is linked, X and Hal are as above defined.

The compound (IIA.1) can be obtained with the known method of the prior art. For example when $X = \text{NH}$, it can be obtained from the corresponding hydroxy-aminoacid, protecting the aminic group by the corresponding ter-butyloxycarbonyl derivative and transforming the hydroxyl function into halogen group as described for the halogenation of the compound (IA.1b) in 2a.1. The free carboxylic function of the compound resulting from the reaction with the molecule of the drug precursor is reacted with the function present in the molecule of the precursor compound of B_1 , as previously illustrated in 1a.1 for the reaction between the R-COOH acid and the precursor compound of B . In the final step the halogen atom (Hal) present on the radical X'_1 is substituted with an ONO_2 group by adding AgNO_3 to an organic solution of the compound. The reaction scheme is the following, exemplified starting from the RCOCl acid halide:

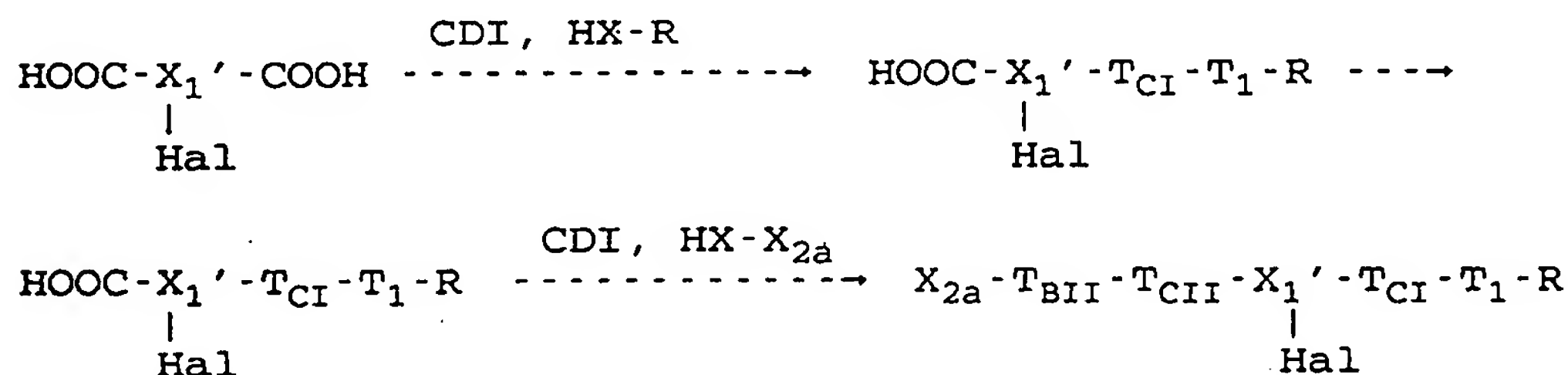


- 1b. When the drug precursor and the precursor compound of B_1 contain each a reactive group of general formula XH , the

two groups in each of the two molecules being equal to or different from each other, wherein X is as above defined, the synthesis is carried out starting from an halogenacid compound of formula



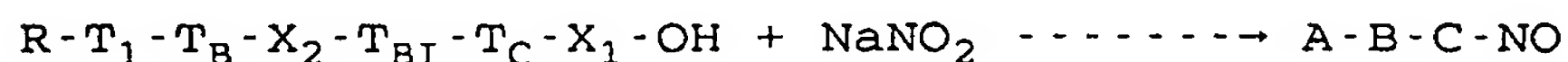
X_1' being as above defined, said compound being prepared from the corresponding hydroxy-diacid as described for the halogenation of the compound (1A.1b) in 2a.1. The halogendiacid compound is treated with an equimolar amount of an agent activating the carboxyl group, under the conditions previously described in 1a.1., and then it is reacted with the reactive function of the drug precursor molecule. In the subsequent step the second carboxylic function is treated with an activating agent, as previously made for the first, and reacted with the precursor compound of B_1 according to the following scheme:



The halogen atom is then substituted with the ONO_2 group as above mentioned.

3. Synthesis of the nitroso ($s=1$) derivatives of formula (I).

3a.1 The compound of formula (1A.1b) wherein $R_3 = OH$ is reacted with sodium nitrite in a solvent formed of a mixture of water with tetrahydrofuran in the presence of hydrochloric acid. The reaction is widely illustrated in the prior art. The general scheme is the following:



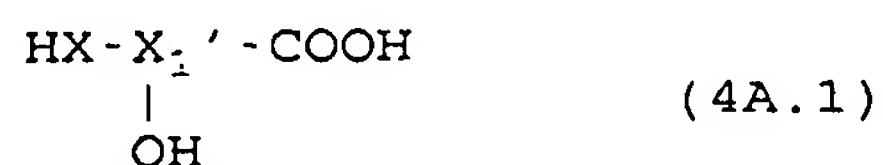
3a.2 If the compound obtained at the end of step A in 1a.2 has formula (IA.2) the corresponding nitroso derivative is obtained treating an hydroxyacid of formula $HO-X_1-COOH$, X_1 being as above defined, first with an agent activating the carboxyl group, as described in 1a.1, then reacting it with 1A.2 and the resulting product with sodium nitrite as described in 3a.1.

3b.1 To obtain the nitroso derivative starting from the compound of formula $R-T_1-T_B-X_2-XH$ (1B.1) obtained at the end of the synthesis described in 1b.1, the compound (1B.1) is reacted with an hydroxyacid as described in 3a.2.

3b.2 To obtain the nitroso derivative from the compound of formula $R-T_1-T_B-X_2-COOH$ (1B.2) obtained at the end of the synthesis described in 1b.2, the acid is transformed into the sodic salt and reacted with a compound $Hal-X_1-OH$, as previously described, and the obtained alcohol is treated as described in 3a.1.

4) Synthesis of the nitroso derivatives of formula (II)

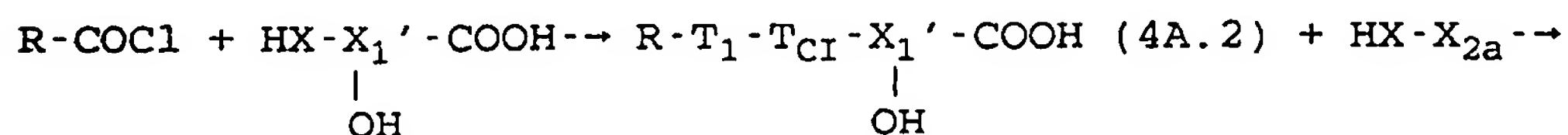
4a.1 When the drug is of formula R-COOH and the precursor compound of B₁ contains only one function reactive group of formula XH, X being as above defined, R-COOH is initially converted into the corresponding acyl-halide or treated with an agent activating the carboxyl group as described in 1a.1, and then reacted with the HX function of an hydroxy-acid compound, said function being equal to or different from that present on the precursor compound of B₁, said hydroxy-acid having the formula:

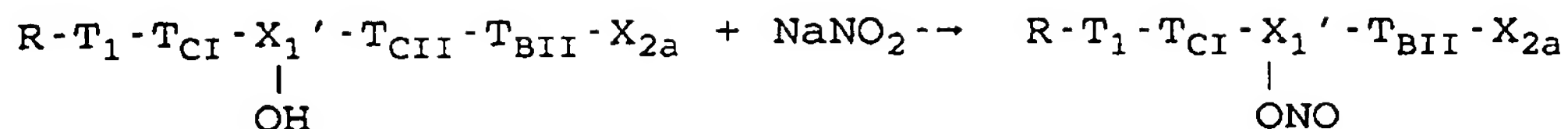


wherein X₁' is Y' as above defined without the oxygen atom through which the -NO group is linked, X is as above defined.

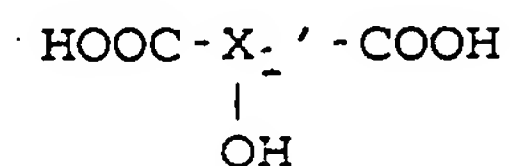
The free carboxylic function of the compound resulting from the reaction with the drug molecule is reacted with the function present in the molecule of the precursor compound of B₁, as previously illustrated in 1a.1 for the reaction between the R-COOH acid and the precursor compound of B. In the final step the alcohol is transformed into the nitroso-derivative as described in 3a.1.

The reaction scheme is the following, exemplified starting from the RCOCl acid halide:

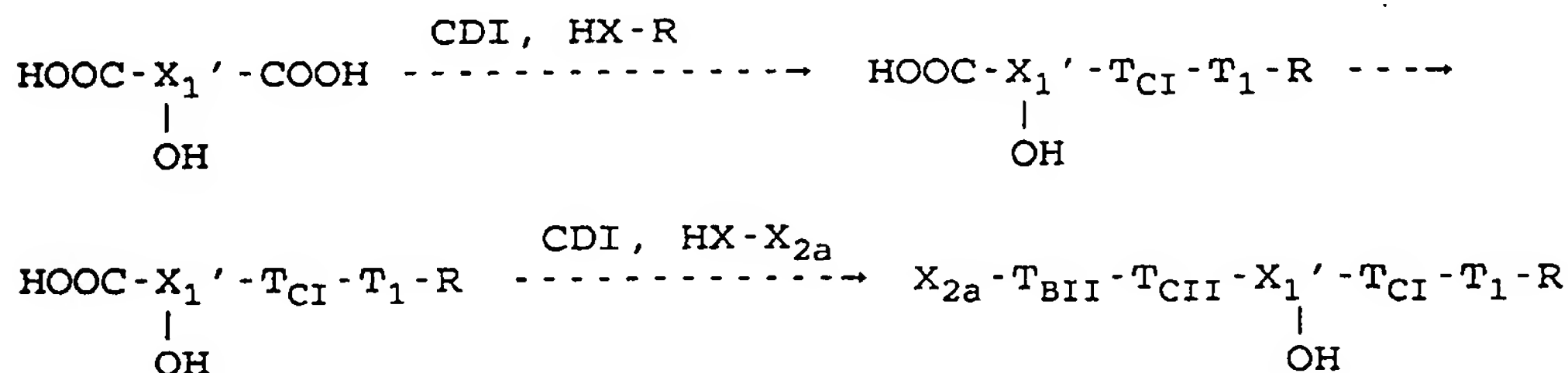




4b. When the drug and the precursor compound of B₁ contain each a reactive group of general formula XH, the two groups in each of the two molecules being equal to or different from each other, wherein X is as above defined, the synthesis is carried out starting from an hydroxydiacid compound of formula



X₁' being as above defined, said hydroxydiacid compound is treated with an equimolar amount of an agent activating the carboxyl group, under the conditions previously described in 1a.1., and then it is reacted with the reactive function of the drug molecule. In the subsequent step the second carboxylic function is treated with an activating agent, as previously made for the first one, and reacted with the precursor compound of B₁ according to the following scheme:



The obtained compound is reacted as described in 3a.1.

The compounds object of the present invention are formulated in the corresponding pharmaceutical compositions for parenteral, oral and topic use according to the well known methods in the art, together with the usual excipients; see for example the volume "Remington's Pharmaceutical Sciences 15a Ed."

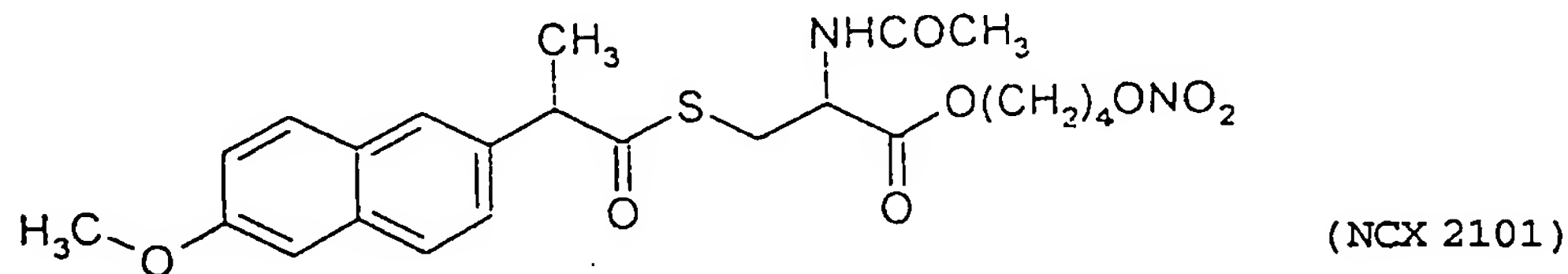
The amount on molar basis of the active principle in these formulations is the same, or lower, in comparison with that used of the corresponding precursor drug.

The daily administrable doses are those of the precursor drugs, or in the case lower. The daily doses can be found in the publications of the field, such as for example in "Physician's Desk reference".

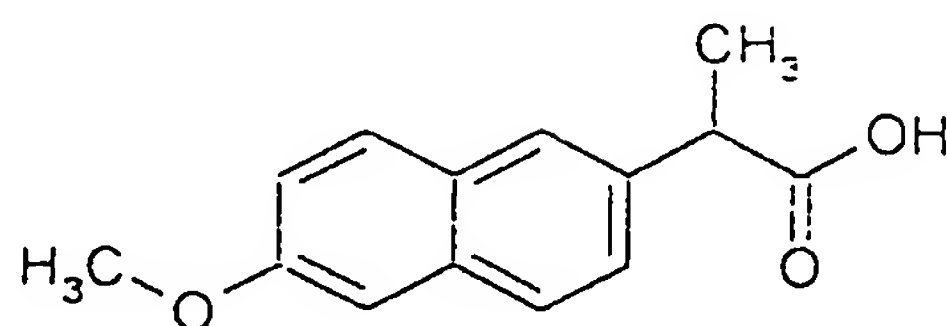
The following examples have the purpose to illustrate the invention and are not to be considered as limitative of the same.

EXAMPLE 1

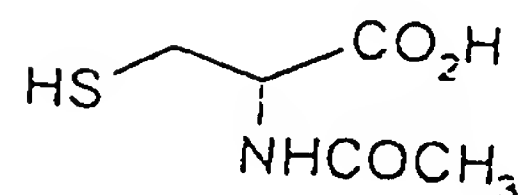
Synthesis of (S,S)-N-acetyl-S-(6-methoxy- α -methyl-2-naphthalen acetyl)cysteine 4-(nitroxy)butyl ester (NCX 2101) having formula



The precursor is naproxene (Formula VI), the precursor of B is N-acetylcysteine (formula CVIII)



(VI)



(CVIII)

a) Synthesis of (S,S)-N-acetyl-S-(6-methoxy-α-methyl-2-naphthalen acetyl)cysteine

To a solution of 6-methoxy-α-methyl-2-naphthalenacetic acid (10 g, 43.4 mmol) in chloroform (100 ml) and N,N-dimethylformamide (6 ml), 1,1'-carbonyldiimidazole (CDI) (7.04 g, 43.4 mmol) is added. After 15 minutes the obtained solution is treated with (S)-N-acetylcysteine (7.08 g, 43.4 mmol) and left at room temperature for 12 hours. The reaction mixture is washed with HCl 5%, then with water and lastly with brine. The organic phase is anhydriified with sodium sulphate and then evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with ethyl acetate. 11.66 g of the expected product in the form of a white solid m.p. 122°-126°C, is obtained.

¹H-NMR (CDCl₃): 7.71-7.65 (3H, m), 7.34 (1H, dd), 7.16-7.09 (2H, m), 6.36 (1H, d), 4.67 (1H, m), 4.00 (1H, q), 3.90 (3H, s) 3.32 (2H, t), 1.84 (3H, s), 1.59 (3H, d).

b) Synthesis of (S,S)-N-acetyl-S-(6-methoxy-α-methyl-2-napht-

halen acetyl)cysteine 4-(bromobutyl) ester

To a solution of (S,S)-N-acetyl-S-(6-methoxy- α -methyl-2-naphthalenacetyl)cysteine (11.3 g, 30.1 mmol) in tetrahydrofuran (200 ml), triphenylphosphine (23.7 g, 90.3 mmol) and carbon tetrabromide (28.85 g, 90.3 mmol) are added. The reaction mixture is left under stirring for 24 hours at room temperature. The solvent is removed by evaporation at reduced pressure. The obtained crude product is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 4 g of the ester in the form of a white solid with m.p. 67°-71°C, are obtained.

c) Synthesis of (S,S)-N-acetyl-S-(6-methoxy- α -methyl-2-naphthalen acetyl)cysteine 4-(nitroxy)butyl ester

To a solution of the ester obtained at the end of the previous step (1 g, 1.96 mmol) in acetonitrile (20 ml), silver nitrate (0.66 g, 3.92 mmol) is added. The reaction mixture is heated for 7 hours under reflux away from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 0.47 g of (S,S)-N-acetyl-S-(6-methoxy- α -methyl-2-naphthalenacetyl)cysteine 4-(nitroxy)butyl ester in the form of a white solid m.p. 56-59°C, are obtained.

$^1\text{H-NMR}$ (CDCl_3): 7.80-7.68 (3H, m), 7.37 (1H, d), 7.20-7.13 (2H, m), 6.12 (1H, d) 4.40 (2H, dd), 4.26 (1H, m), 4.15-3.87 (3H,

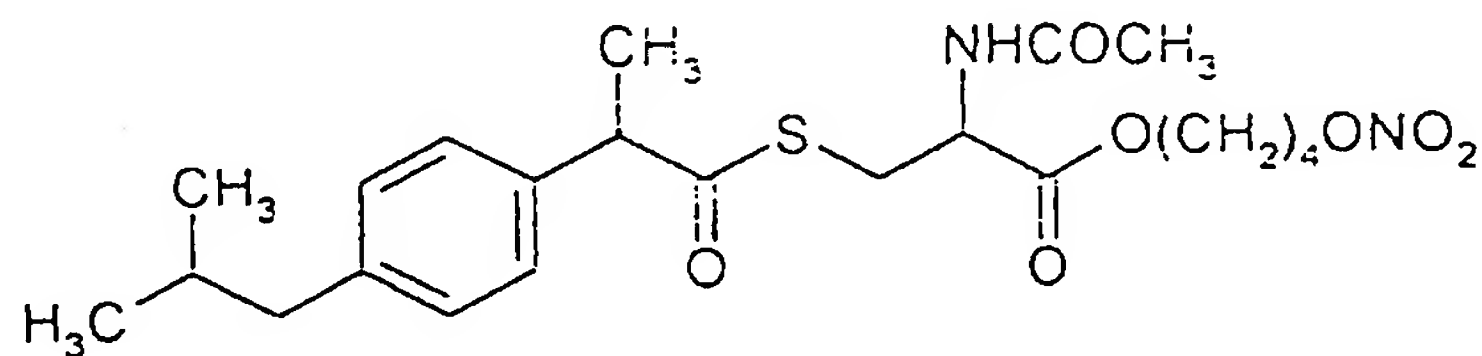
m), 3.92 (3H, s), 3.33 (2H, d), 1.86 (3H, d), 1.74-1.67 (4H, m), 1.61 (3H, d).

Elementary analysis:

Calculated C:	56.08%	H: 5.73%	N: 5.71%	S: 6.51%
Found C:	55.99%	H: 5.68%	N: 5.60%	S: 6.35%

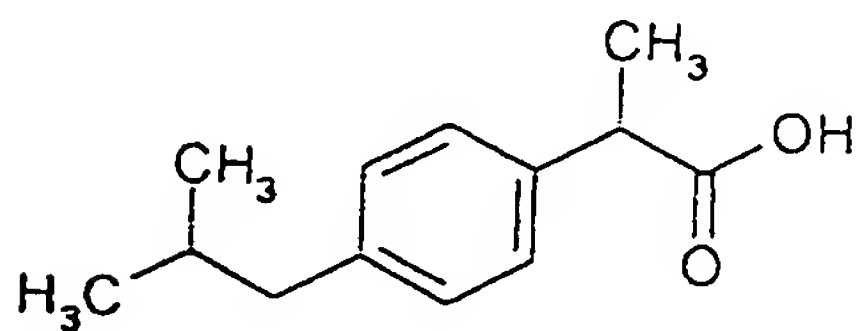
EXAMPLE 2

Synthesis of (S)-N-acetyl-S- $\{\alpha$ -methyl[4-(2-methylpropyl) benzene] acetyl}cysteine 4-(nitroxy)butyl ester (NCX 2111) having formula

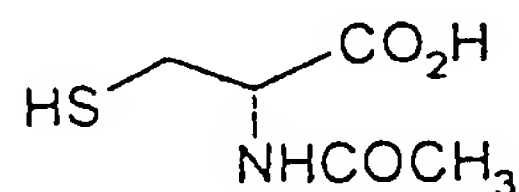


(NCX 2111)

The precursor is ibuprofen (Formula VII), the precursor of B is N-acetylcysteine (formula CVIII)



(VII)



(CVIII)

a) Synthesis of (S)-N-acetyl-S- $\{\alpha$ -methyl[4-(2-methylpropyl) benzene]acetyl}cysteine

To a solution of α -methyl[4-(2-methylpropyl)benzene] acetic acid (10 g, 48.48 mmol) in chloroform (100 ml) and N,N-dimethylformamide (6 ml) 1,1'-carbonyldiimidazole (7.86 g,

48.48 mmol) is added. After 1 hour the obtained solution is treated with (S)-N-acetylcysteine (7.91 g, 48.47 mmol) and left at room temperature for 24 hours. The reaction mixture is washed with HCl 5%, then with water and lastly with brine. The organic phase is anhydriified with sodium sulphate and then evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with ethyl acetate. 13.3 g of the expected product in the form of an oil are obtained.

¹H-NMR (CDCl₃): 10.17 (1H, s) 7.13 (2H, d) 6.54 (1H, d), 4.76 (1H, m), 3.93 (1H, q), 3.42-3.30 (2H, m), 2.49 (2H, d), 1.85-1.83 (4H, m), 1.55 (3H, d), 0.93 (6H, d).

b) Synthesis of (S)-N-acetyl-S-{ α -methyl[4-(2-methylpropyl)-benzene]acetyl}cysteine 4-(bromobutyl) ester

To a solution of (S)-N-acetyl-S-{ α -methyl[4-(2-methylpropyl)benzene]acetyl}cysteine (12.8 g, 36.4 mmol) in tetrahydrofuran (100 ml), triphenylphosphine (28.65 g, 109.23 mmol) and carbon tetrabromide (36.23 g, 109.23 mmol) are added. The reaction mixture is let under stirring for 48 hours at room temperature. The solvent is removed by evaporation at reduced pressure. The crude product is purified by chromatography on silica gel eluting with cyclohexane/ethyl acetate 1/1. 5.79 g of the ester in the form of an oil are obtained.

c) Synthesis of (S)-N-acetyl-S-{ α -methyl[4-(2-methylpropyl)

benzene]acetyl}cysteine 4-(nitroxy)butyl ester

To a solution of the ester obtained at the end of the previous step (5.5 g, 11.3 mmol) in acetonitrile (100 ml) silver nitrate (2.69 g, 15.8 mmol) is added. The reaction mixture is heated for 24 hours under reflux away from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with cyclohexane/ethyl acetate 7/3. 1.18 g of (S)-N-acetyl-S- $\{\alpha$ -methyl[4-(2-methylpropyl)benzene]acetyl}cysteine 4-(nitroxy)butyl ester in the form of an oil are obtained.

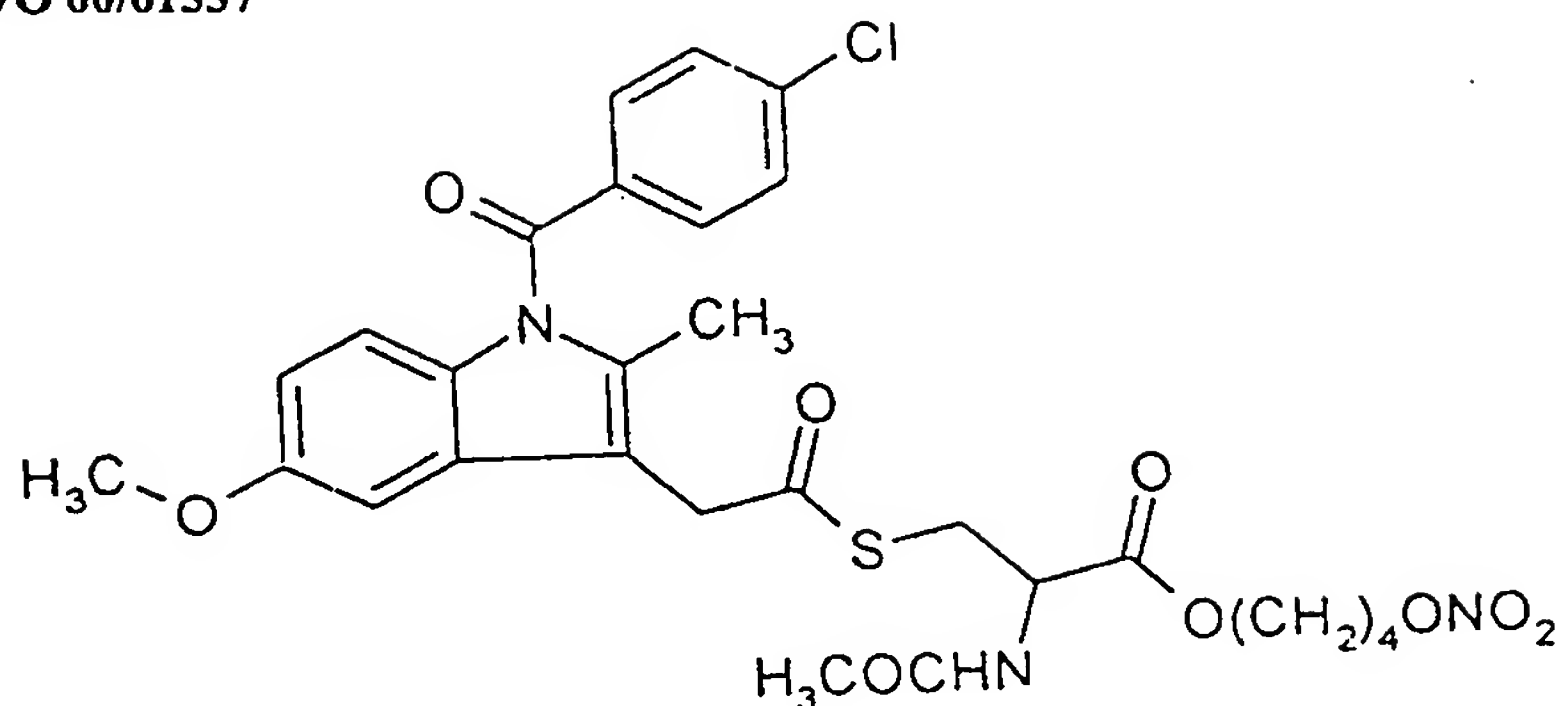
$^1\text{H-NMR}$ (CDCl_3): 7.27-7.09 (4H, m), 6.19 (1H, d), 4.75 (1H, m), 4.47 (2H, t), 4.15-4.02 (2H, m), 3.86 (1H, q), 3.31 (2H, d), 2.44 (2H, d), 1.89 (3H, d), 1.86-1.76 (5H, m), 1.51 (3H, d), 0.89 (6H, d).

Elementary analysis:

Calculated	C: 56.39%	H: 6.88%	N: 6.00%	S: 6.84%
Found	C: 56.22%	H: 6.79%	N: 5.88%	S: 6.92%

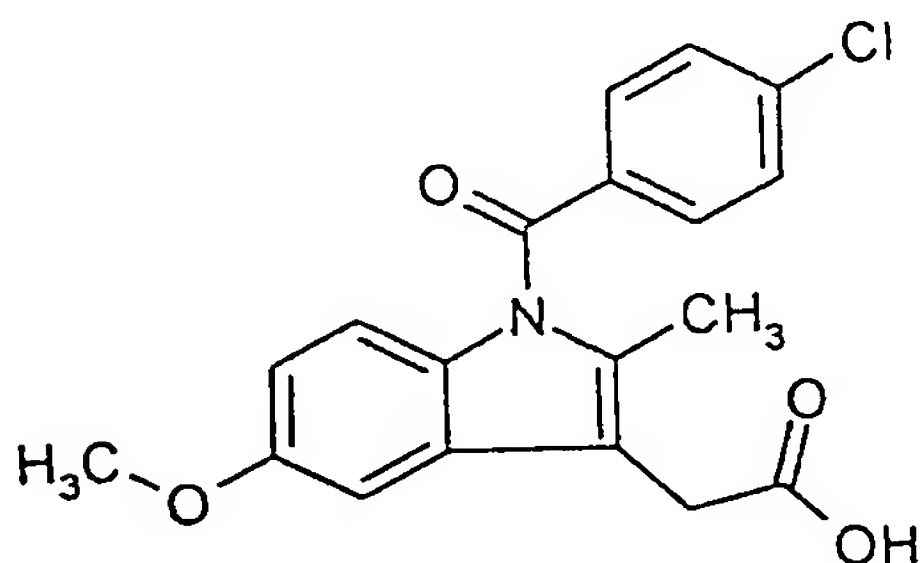
EXAMPLE 3

Synthesis of (S)-N-acetyl-S-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetyl]cysteine 4-(nitroxy)butyl ester (NCX 2121) having formula

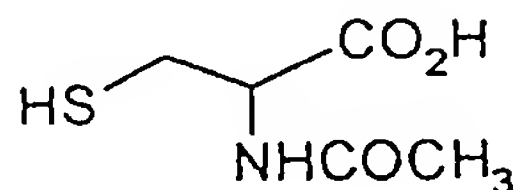


(NCX 2121)

The precursor is indomethacin (Formula VIII), the precursor of B is N-acetylcysteine (formula CVIII)



(VIII)



(CVIII)

a) Synthesis of (S)-N-acetyl-S-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetyl]cysteine

To a solution of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid (10 g, 28.00 mmols) in chloroform (100 ml) and N,N-dimethylformamide (2 ml) 1,1'-carbonyldiimidazole (4.53 g, 28.00 mmols) is added. After 1 hour the obtained solution is treated with (S)-N-acetylcysteine (4.56 g, 28.00 mmols) and left at room temperature for 24 hours. The reaction mixture is washed with HCl 5%, then with water and lastly with brine. The organic phase is anhydriified with sodium sulphate

and then evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with ethyl acetate. 7.79 g of the expected product in the form of a yellow solid m.p. 129°C, are obtained.

¹H-NMR (DMSO-d₆): 12.90 (1H, s), 8.21 (1H, d), 7.69-7.64 (4H, m), 7.06 (1H, d), 6.96 (1H, d), 6.73 (1H, dd), 4.33 (1H, m), 4.02 (2H, s), 3.77 (3H, s), 3.33-2.96 (2H, m), 2.22 (3H, s), 1.78 (3H, s).

b) Synthesis of (S)-N-acetyl-S-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetyl]cysteine 4-(bromobutyl) ester

To a solution of (S)-N-acetyl-S-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetyl]cysteine (3.09 g, 6.14 mmol) in N,N dimethylformamide (50 ml), sodium ethylate (0.42 g, 6.14 mmol) and, after 30 minutes, 1,4-dibromobutane (2.18 ml, 18.00 mmol) dissolved in 25 ml of N, N dimethylformamide, are added. The reaction mixture is left under stirring for 20 hours at room temperature, then it is diluted with ethyl ether and washed with water. After the organic phase has been anhydriified with sodium sulphate, the solvent is removed by evaporation at reduced pressure. The obtained crude product is purified by chromatography on silica gel, eluting with cyclohexane/ethyl acetate 1/1. 1.7 g of the ester in the form of a yellow solid with m.p. 130°-134°C are obtained.

c) Synthesis of (S)-N-acetyl-S-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetyl]cysteine 4-(nitroxy)butyl ester

To a solution of the ester obtained at the end of the previous step (1.6 g, 2.5 mmol) in acetonitrile (30 ml) silver nitrate (0.6 g, 3.51 mmol) is added. The reaction mixture is heated for 8 hours under reflux away from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with cyclohexane/ethyl acetate 4/6. 1.2 g of (S)-N-acetyl-S-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetyl]cysteine 4-(nitroxy)butyl ester in the form of an oil are obtained.

$^1\text{H-NMR}$ (CDCl_3): 7.66 (2H, d), 7.48 (2H, d), 6.90 (2H, m), 6.68 (1H, m), 6.14 (1H, d), 4.77 (1H, m), 4.43 (2H, t), 4.08 (2H, m), 3.87 (2H, s), 3.83 (3H, s), 3.34 (2H, d), 2.38 (3H, s), 1.90 (3H, s), 1.78-1.70 (4H, m).

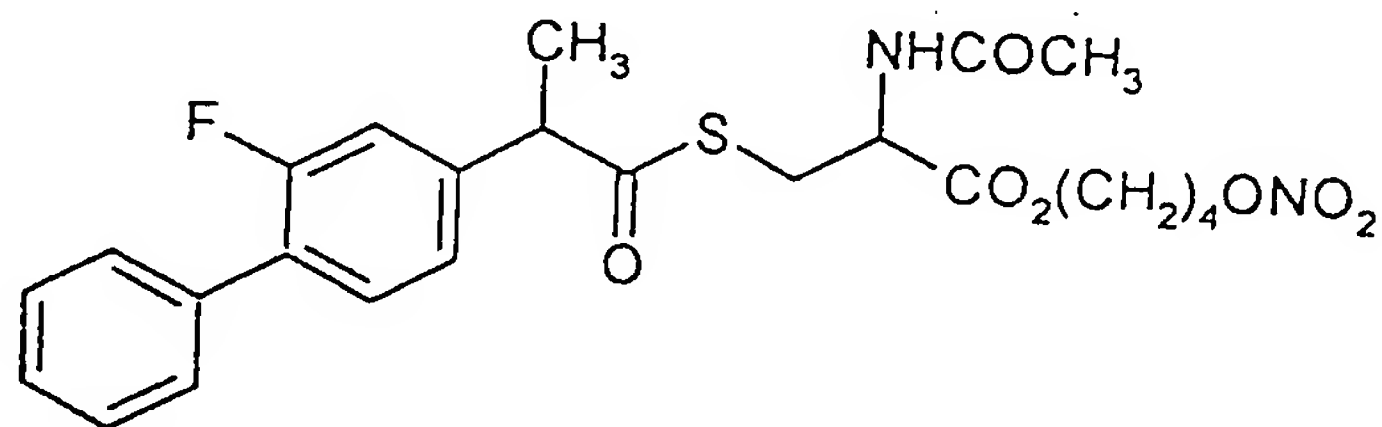
Elementary analysis:

Calculated C: 54.24% H: 4.88% N: 6.80% S: 5.17% Cl: 5.72%

Found C: 54.32% H: 4.93% N: 6.91% S: 5.13% Cl: 5.84%

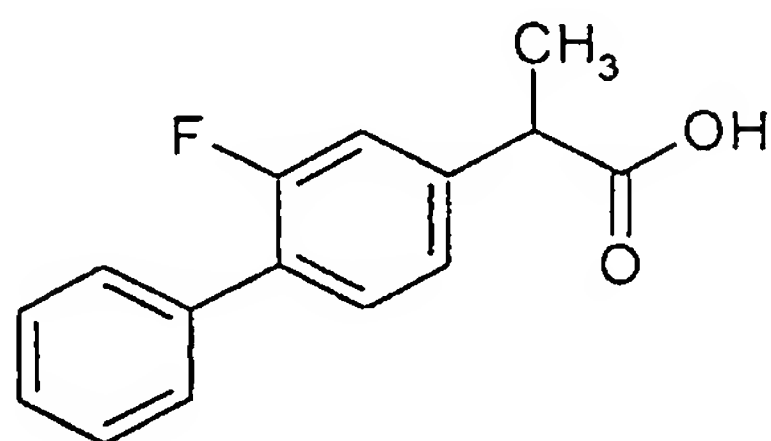
EXAMPLE 4

Synthesis of (S)-N-acetyl-[2-fluoro- α -methyl-(1,1'-biphenyl)-4-acetyl]cysteine 4-(nitroxy)butyl ester (NCX 2131) having formula

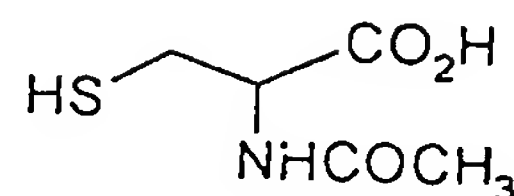


(NCX2131)

The precursor is flurbiprofen (Formula IX), the precursor of B is N-acetylcysteine (formula CVIII)



(IX)



(CVIII)

The NCX 2131 compound is synthesized according to the process described in Example 1. The substance appears as an oil. Yield: 26%

¹H-NMR (CDCl₃): 7.41-7.38 (6H, m), 7.10 (2H, m), 6.22 (1H, d), 4.78 (1H, m), 4.46 (2H, t), 4.13 (2H, t), 3.92 (1H, q), 3.36 (2H, d), 1.93 (3H, d), 1.76 (4H, d), 1.55 (3H, d).

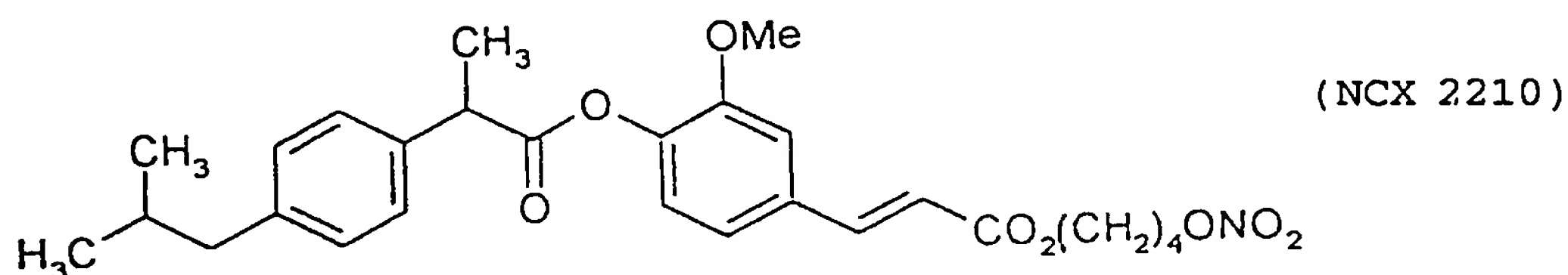
Elementary analysis

Calculated C: 56.91% H: 5.37% N: 5.55% S: 6.33% F: 3.75%

Found C: 56.99% H: 5.41% N: 5.66% S: 6.41% F: 3.83%

EXAMPLE 5

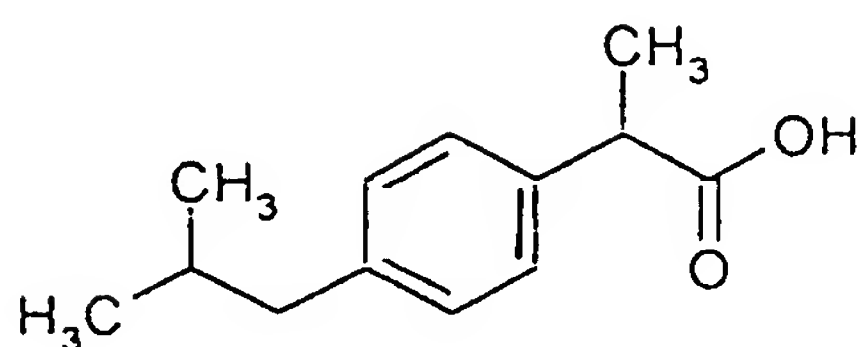
Preparation of trans-3-[4-[α-methyl-[4-(-2-methylpropyl)benzene] acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-(nitroxy) butyl ester (NCX 2210) having formula:



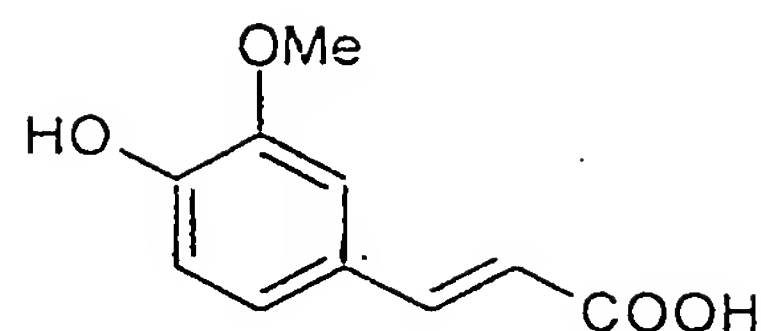
(NCX 2210)

The precursor is ibuprofen (Formula VII), the precursor of

B is ferulic acid (formula DII):



(VII)



(DII)

a) Synthesis of trans-3-[4-[α -methyl-[4-(-2-methylpropyl)benzene]acetyloxy]-3-methoxyphenyl]-2-propenoic acid

To a solution of α -methyl-[4-(2-methylpropyl)benzene]acetic acid (5.03 g, 24.4 mmol) in tetrahydrofuran (100 ml) and N,N-dimethylformamide (5 ml) 1,1-carbonyldiimidazole (4.25 g, 24.8 mmol) is added. After 1 hour the obtained solution is treated with ferulic acid (4.90 g, 25 mmol), sodium ethylate (89 mg) is added and left at room temperature under stirring for 12 hours. The reaction mixture is washed with HCl 5%, then with water and lastly with brine. The organic phase is anhydriified with sodium sulphate and evaporated at reduced pressure.

The obtained residue is purified by chromatography on silica gel, eluting with ethyl acetate/n-hexane 7/3. 5.1 g of trans-3-[4-[α -methyl-[4-(-2-methylpropyl)benzene] acetyl]-3-methoxyphenyl]-2-propenoic acid as white solid, with m.p. 131°-137°C, are obtained.

$^1\text{H-NMR}$ (CDCl_3): 7.72 (1H, d), 7.32 (2H, dd), 7.26 (1H, m), 7.16-7.07 (4H, m), 6.98 (1H, d), 6.37 (1H, d), 3.99 (1H, q),

3.73 (3H, s), 2.47 (2H, d), 1.88 (1H, m), 1.63 (3H, d), 0.92 (6H, d).

b) synthesis of trans-3-[4-[α -methyl-[4-(-2-methylpropyl)-benzene]acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-bromobutyl ester

To a solution of trans-3-[4-[α -methyl-[4-(2-methylpropyl)-benzene]acetyloxy]-3-methoxyphenyl]-2-propenoic acid (5.33 g, 14 mmol) in N,N-dimethylformamide (130 ml), sodium ethylate (1.2 g, 16 mmol) is added under stirring. After 1 hour to the obtained mixture 1,4-dibromobutane (10 g, 46 mmol) is added and let react at room temperature for 12 hours. The reaction mixture is washed with HCl 5%, then with water and lastly with brine, the organic phase is anhydriified with sodium sulphate and evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 4.46 g of trans-3-[4-hydroxy-[α -methyl-[4-(-2-methylpropyl)benzene]acetyl]-3-methoxyphenyl]-2-propenoyl 4-bromobutyl ester are obtained.

c) Synthesis of trans-3-[4-[α -methyl-[4-(-2-methylpropyl)benzene]acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-(nitroxy) butyl ester

To a solution of trans-3-[4-[α -methyl-[4-(-2-methylpropyl)benzene]acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-bromobutyl ester (4 g, 7.72 mmol) in acetonitrile (70 ml) silver nitrate (2.58 g, 15 mmol) is added. The reaction mixture is

heated under reflux for 2 hours away from light. At the end the formed salt is removed by filtration and the solution is evaporated at reduced pressure. The recovered residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 8/2. 2.4 g of trans-3-[4-[α -methyl-[4-(2-methylpropyl)benzene]acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-(nitroxy) butyl ester as an oil, are obtained.

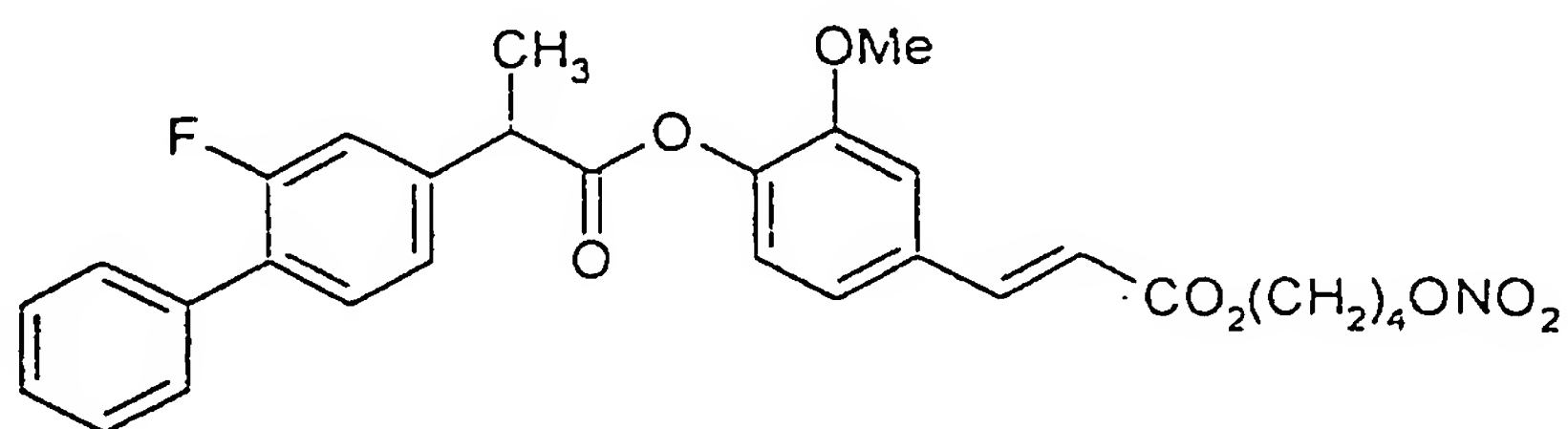
$^1\text{H-NMR}$ (CDCl_3): 7.62 (1H, d), 7.32 (2H, d), 7.15 (2H, d), 7.16-7.05 (2H, m), 6.96 (1H, d), 6.35 (1H, d), 4.51 (2H, t), 4.24 (2H, t), 3.99 (1H, q), 3.74 (3H, s), 2.48 (2H, d), 1.89-1.83 (5H, m), 1.62 (3H, d), 0.92 (6H, d).

Elementary analysis:

Calculated	C: 64.91%	H: 6.66%	N: 2.82%
Found	C: 64.83%	H: 6.52%	N: 2.69%

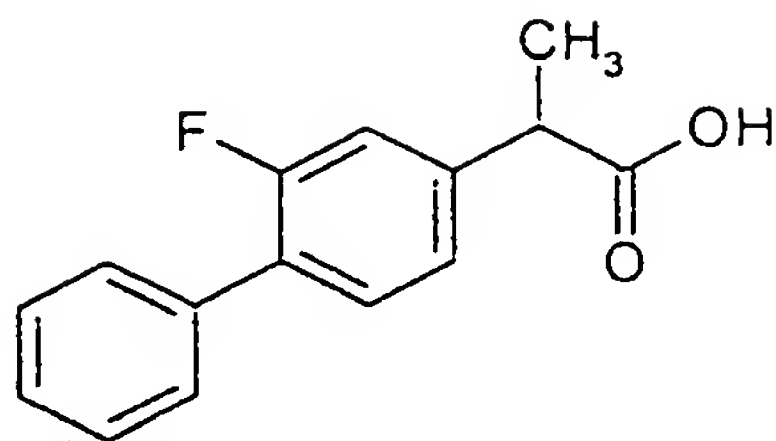
EXAMPLE 6

Synthesis of trans-3-[4-[2-fluoro- α -methyl-(1,1'-biphenyl)-4-acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-(nitroxy) butyl ester (NCX 2216) having formula:

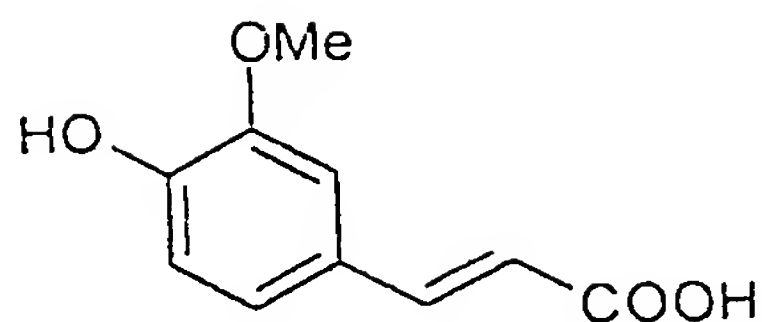


(NCX2216)

The precursor is flurbiprofen (formula IX), the precursor of B is ferulic acid (formula DII)



(IX)



(DII)

The NCX 2216 compound is synthesized according to the process described in Example 5. The total process yield is 32%. The substance appears as an amorphous solid.

^1H - NMR (CDCl_3): 7.40-7.25 (9H, m), 7.07-7.01 (2H, d), 6.98 (1H, m), 6.38 (1H, d), 4.44 (2H, t), 4.46 (2H, t), 4.21 (2H, t), 4.04 (1H, q), 3.73 (3H, s), 1.72 (4H, m), 1.65 (3H, d).

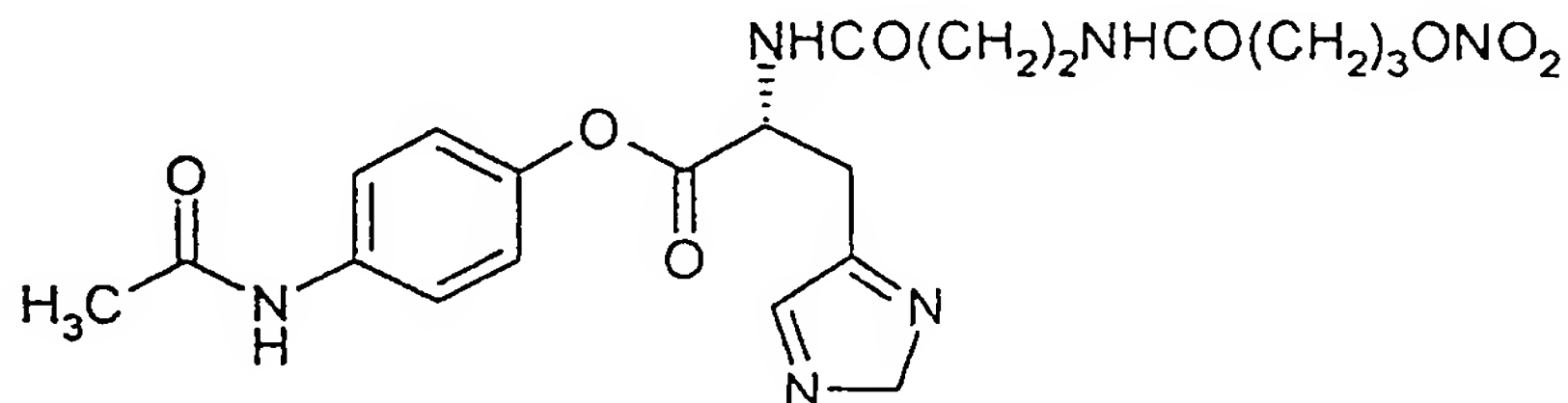
Elementary analysis:

Calculated C: 64.79% H: 5.25% N: 2.62% F: 3.53%

Found C: 64.85% H: 5.31% N: 2.74% F: 3.48%

EXAMPLE 7

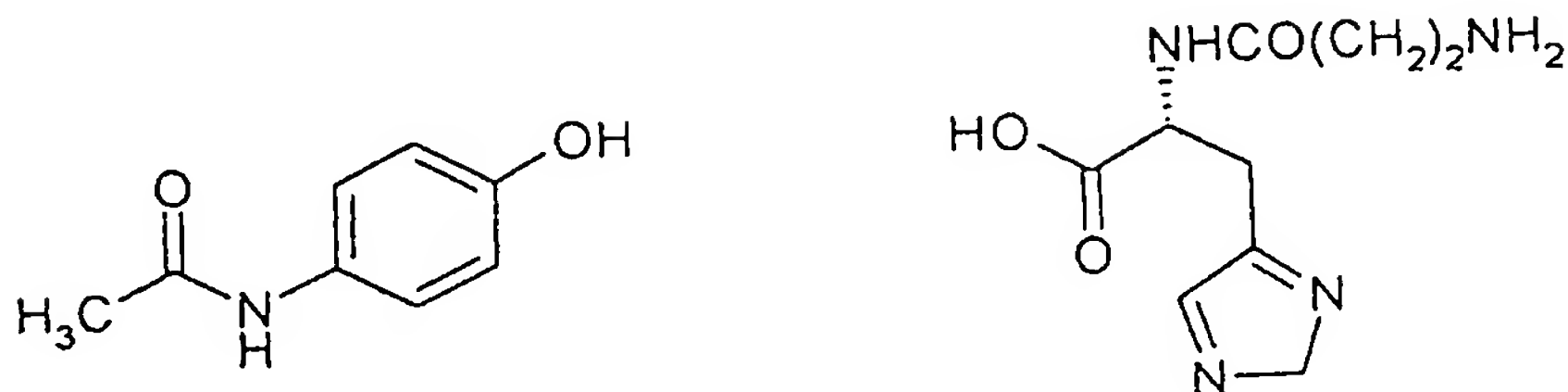
Preparation of N-(4-nitroxybutyryl)- β -alanyl (L)-histidine 4-acetamido phenyl ester (NCX 2160) having formula:



(NCX 2160)

wherein the precursor is acetaminofen (paracetamol) having

formula (X) and the precursor of B is (L)-carnosine (NCX 2053) having formula (CI):



(X)

(CI)

a) Synthesis of N-(4-bromobutyryl)- β -alanyl (L)-histidine

To a solution of carnosine (5 g, 22.1 mmol) in N,N-dimethylformamide (80 ml), triethylamine (4.62 ml, 33.1 mmol) and 4-bromobutyrylchloride (chloride of 4-bromobutyric acid - 83.85 ml, 33.1 mmol) are added. The solution is left under stirring for 24 hours at room temperature, then it is diluted with ethyl acetate and the organic phase is washed with water. The organic phase is then anhydriified with sodium sulphate and evaporated at reduced pressure. The obtained crude product is purified by chromatography on silica gel eluting with ethyl acetate, obtaining the final product.

b) synthesis of N-(4-bromobutyryl)- β -alanyl (L)-histidine 4-acetamidophenyl ester

To a solution of N-(4-bromobutyryl)- β -alanyl (L)-histidine (3 g, 8 mmol) in chloroform (50 ml) and N,N-dimethylformamide (4 ml), paracetamol (1.21 g, 8 mmol), N,N-dicyclohexylcarbodiimide (1.65 g, 8 mmol) and dimethylaminopyridine (0.04

g, 0.36 mmoles) are added under stirring. The mixture is let react at room temperature for 6 hours. Lastly it is filtered, diluted with chloroform and washed with water. The organic phase is anhydriified with sodium sulphate and evaporated at reduced pressure. The obtained crude product is purified by chromatography on silica gel, eluting with ethyl acetate/n-hexane 7/3. N-(4-bromobutyryl)- β -alanyl (L)-histidine 4-acetamido phenyl ester is obtained.

c) Synthesis of N-(4-nitroxybutyryl)- β -alanyl (L)-histidine 4-acetamidophenyl ester

To a solution of N-(4-bromobutyryl)- β -alanyl (L)-histidine 4-acetamido phenyl ester (4 g, 7.87 mmoles) in acetonitrile (70 ml), silver nitrate (1.87 g, 11 mmoles) is added under stirring. The reaction mixture is heated for 5 hours under reflux, away from light. At the end the formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 3/7. The expected product is obtained with an yield of 17%.

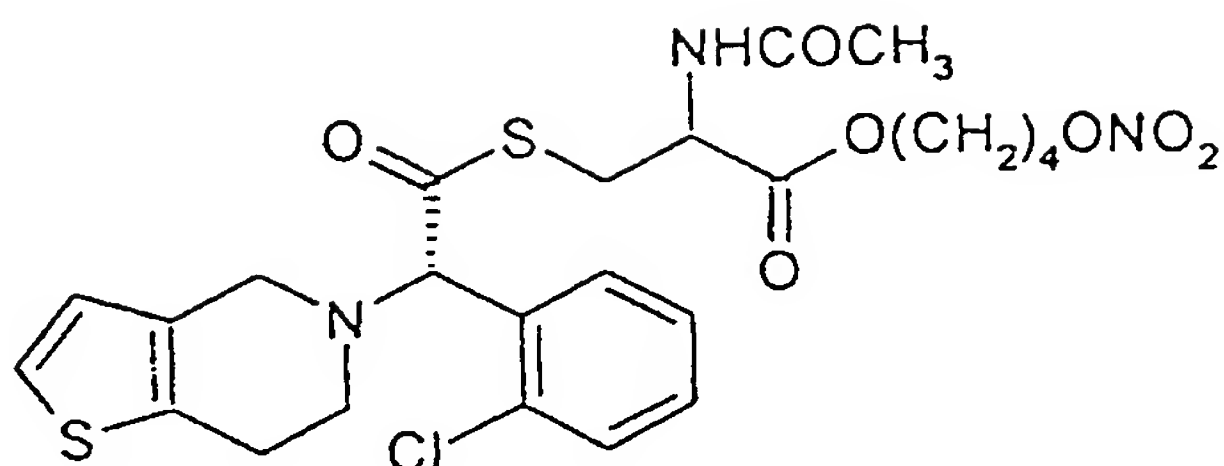
Elementary analysis:

Calculated	C: 51.39%	H: 5.34%	N:17.19%
Found	C: 51.28%	H: 5.28%	N:17.06%

EXAMPLE 8

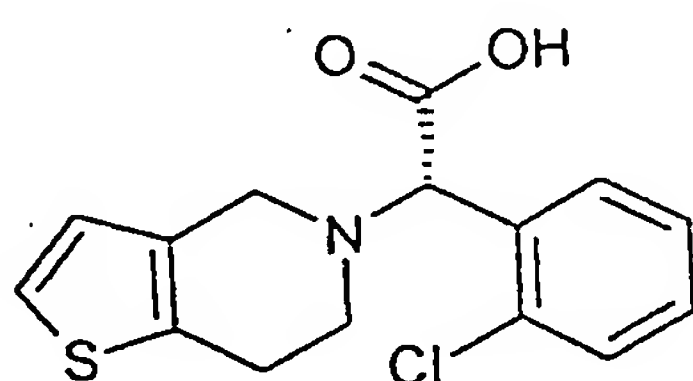
Preparation of N-acetyl-S-[(S)- α -(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridin-5(4H)acetyl] (S)-cysteine 4-(nitroxy)

butyl ester (NCX 2136)

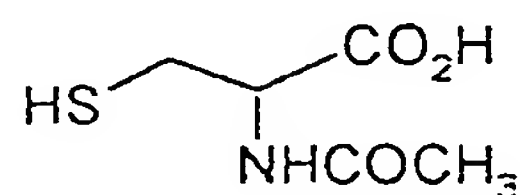


(NCX 2136)

wherein the precursor is clopidogrel having formula (XI) and the precursor of B is N-aceticysteine having formula (CVIII):



(XI)



(CVIII)

The compound is synthesized following the procedure reported in Example 1. The yield is of 23%.

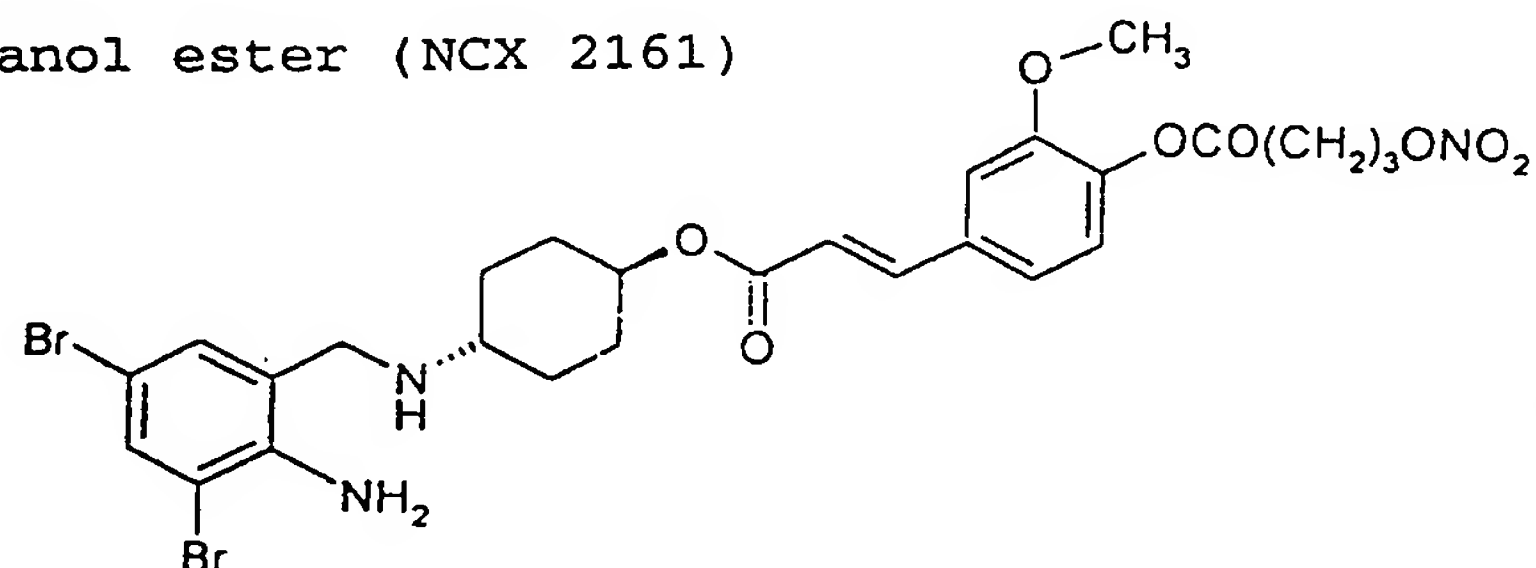
Elementary analysis:

Calculated C: 50.55% H: 4.95% N: 7.40% S: 11.24% Cl: 6.22%

Found C: 50.70% H: 4.99% N: 7.60% S: 11.20% Cl: 6.15%

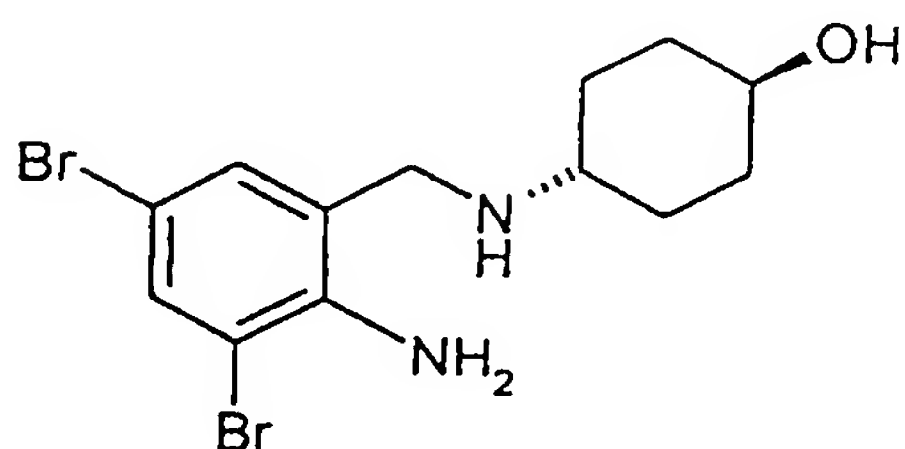
EXAMPLE 9

Preparation of [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-trans-propenoyl-4-[(2-amino-3,5-dibromophenyl)methylamino]cyclohexanol ester (NCX 2161)

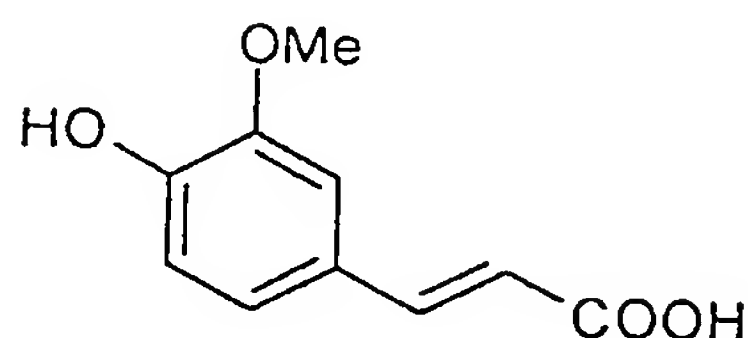


(NCX2161)

wherein the precursor is ambroxol having formula (XII) and the precursor of B is represented by ferulic acid having formula (DII):



(XII)



(DII)

a) Synthesis of 4-[(2-ter-butoxycarbonylamino-3,5-dibromophenyl)methylamino] trans cyclohexanol

To a mixture of 4-[(2-amino-3,5-dibromophenyl)methylamino]cyclohexanol (5 g, 13.22 mmoles) in dioxane (35 ml) and water (50 ml), triethylamine (3.31 ml, 23.7 mmoles) and di-ter-butylidicarbonate (3.46 g, 15.86 mmoles) are added under stirring. After 24 hours the solution is concentrated under vacuum, a HCl 1% solution until neutral pH (pH=7) is added and the organic phase is extracted with ethyl acetate. The organic phase is anhydriified with sodium sulphate and evaporated under vacuum. 4-[(2-ter-butoxycarbonylamino-3,5-dibromophenyl) methyl amino]cyclohexanol is obtained which is used without further purification.

b) Synthesis of (3-methoxy-4-hydroxyphenyl)-2-trans-propenoyl-

4-[(2-ter-butoxycarbonylamino-3,5-dibromo phenyl)methylamino]
cyclohexanol ester

To a solution of ferulic acid (4 g, 20.5 mmol) in tetrahydrofuran (40 ml) cooled at 0°C, 1,1'-carbonyldiimidazole (3.34 g, 20.5 mmol) is added. After 10 minutes the solution is treated with 4-[(2-ter-butoxycarbonylamino-3,5-dibromophenyl) methyl amino]cyclohexanol (9.8 g, 20.5 mmol) and let react at room temperature for 4 hours. The reaction mixture is concentrated under vacuum, treated with methylene chloride, washed with a HCl 1% solution and then with water. The organic phase is anhydriified with sodium sulphate and then evaporated under vacuum. The obtained residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 1/1. (3-methoxy-4-hydroxyphenyl)-2-trans propenoyl 4-[(2-ter-butoxycarbonylamino-3,5-dibromo phenyl) methylamino] cyclohexanol ester, is obtained.

c) Synthesis of [3-methoxy-4-(4-bromobutyryl-oxy)phenyl]-2-trans propenoyl-4-[(2-ter-butoxycarbonylamino-3,5-dibromo-phenyl) methylamino] cyclohexanol ester

To a solution of (3-methoxy-4-hydroxyphenyl)-2-trans propenoyl-4-[(2-ter-butoxycarbonylamino-3,5-dibromo-phenyl) methylamino] cyclohexanol ester (4 g, 6.11 mmol) in tetrahydrofuran (80 ml), triethylamine (0.85 ml, 6.11 mmol) and 4-bromobutyrylchloride (0.7 ml, 6.11 mmol) are added under stirring. It is let react at room temperature for 8 hours and

then the organic solvent is evaporated at reduced pressure. The obtained crude product is treated with ethyl acetate and the organic phase washed with water. The organic phase is anhydrified with sodium sulphate and evaporated under vacuum. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. [3-methoxy-4-(4-bromobutyryloxy)-phenyl]-2-trans propenoyl 4-[(2-ter-butoxycarbonylamino-3,5-dibromo phenyl) methylamino] cyclohexanol ester is obtained.

d) Synthesis of [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-trans-propenoyl 4-[(2-ter-butoxycarbonylamino-3,5-dibromo phenyl) methylamino] cyclohexanol ester

To a solution of [3-methoxy-4-(4-bromobutyryloxy)phenyl]-2-trans-propenoyl-4-[(2-ter-butoxycarbonylamino-3,5-dibromo-phenyl)methylamino] cyclohexanol ester (4 g, 4,98 mmols) in acetonitrile (70 ml), silver nitrate (0.87 g, 4.98 mmols) is added under stirring. It is heated under reflux for 7 hours away from light and lastly the formed salt is removed by filtration. The organic solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-transpropenoyl 4-[(2-ter-butoxycarbonylamino-3,5-dibromo-phenyl)methylamino] cyclohexanol ester is obtained.

e) Synthesis of [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-

transpropenoyl 4-[(2-amino-3,5-dibromo phenyl) methylamino]
cyclohexanol ester

To a solution of [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-transpropenoyl 4-[(2-ter-butoxycarbonylamino-3,5-dibromo phenyl)-methylamino] cyclohexanol ester (2 g, 2.54 mmol) in ethyl acetate (50 ml), cooled at 0°C and maintained under stirring, a HCl 5N solution in ethyl acetate (3.17 ml) is added. The solution is left under stirring at 0°C for 4 hours. Lastly the precipitate is filtered. The obtained crude product is treated with ethyl acetate, to which a 5% sodium bicarbonate solution is added. It is shaken and the bicarbonate solution is substituted with an equal part of water. It is shaken again, the organic phase is recovered, anhydriified with sodium sulphate and evaproated at reduced pressure. [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-transpropenoyl-4-[(2-amino-3,5-dibromophenyl) methylamino] cyclohexanol ester is obtained.
Yield: 36%

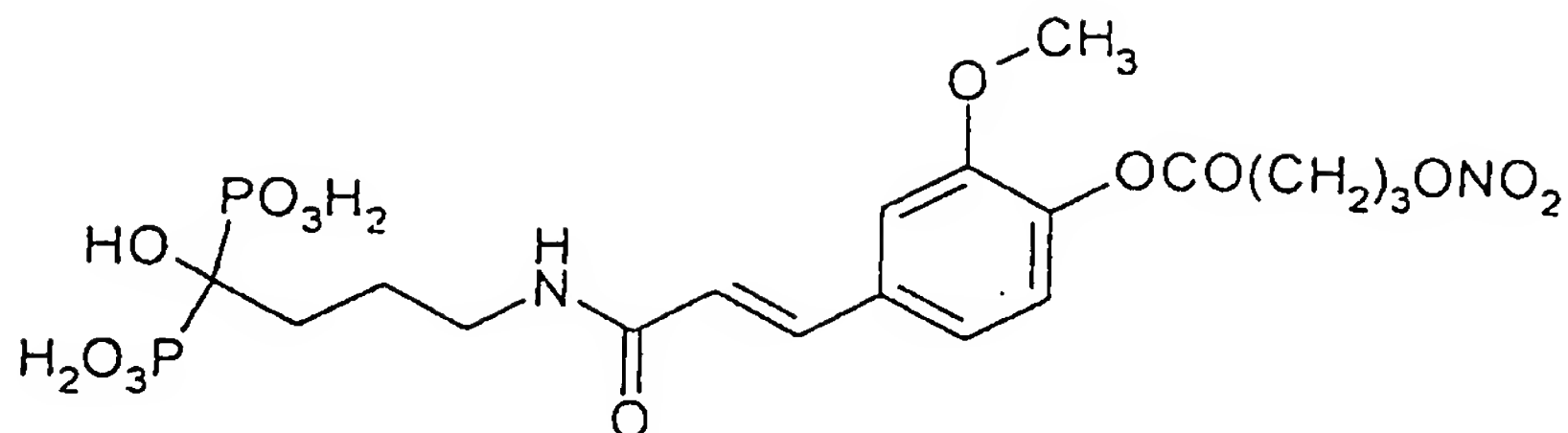
Elementary analysis:

Calculated C: 47.30% H: 4.56% N: 6.15% Br: 23.31%

Found C: 47.26% H: 4.53% N: 6.00% Br: 23.42%

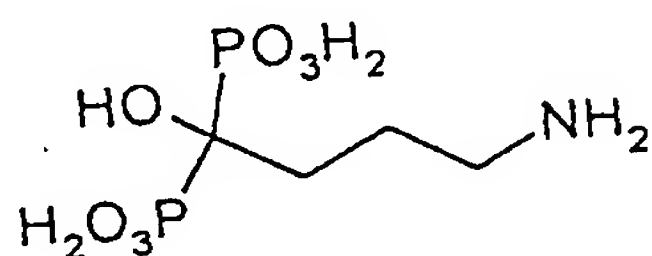
EXAMPLE 10

Preparation of [4-amino-[[3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-trans propenoyl]-1-hydroxy-butyliden]-bisphosphonic acid (NCX 2211),

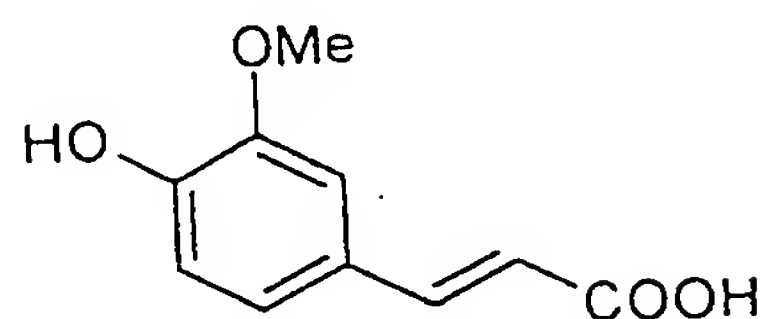


(NCX 2211)

wherein the precursor is alendronic acid of formula (XIII) and the precursor of B is the ferulic acid (formula DII):



(XIII)



(DII)

a) Synthesis of [3-methoxy-4-(4-bromobutyryloxy)phenyl]-2-trans-propenoic acid

To a solution of ferulic acid (1.2 g, 6.11 mmols) in tetrahydrofuran (80 ml), triethylamine (0.85 ml, 6.11 mmols) and 4-bromobutyrylchloride (0.7 ml, 6.11 mmols) are added under stirring. It is let react at room temperature for 3 hours and then evaporated at reduced pressure. The obtained crude product is treated with ethyl acetate and the organic phase washed with water. The organic phase is then anhydriified with sodium sulphate and evaporated under vacuum. The obtained residue is purified by chromatography on silica gel eluting

with chloroform/methanol 8/2. The [3-methoxy-4-(4-bromobutyryloxy)-phenyl]-2-trans propenoic acid is lastly isolated.

b) Synthesis of the [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-trans propenoic acid

To a solution of [3-methoxy-4-(4-bromobutyryloxy)phenyl]-2-trans-propenoic acid (1.5 g, 4.5 mmol) in acetonitrile (70 ml) silver nitrate (0.87 g, 4.98 mmol) is added under stirring. The mixture is heated under reflux and, under stirring, it is reacted for 3 hours sheltered from the light. The formed salt is removed by filtration and the organic phase is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel column, eluting with chloroform/methanol 8/2. The [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-trans propenoic acid is recovered.

c) Synthesis of [4-amino-[[3-methoxy-4-(4-nitroxy butyryloxy)phenyl]-2-trans propenoyl]-1-hydroxy-butyliden] bisphosphonic acid

To a solution of [3-methoxy-4-(4-nitroxybutyryloxy)-phenyl]-2-trans propenoic acid (2g, 6.4 mmol) in N,N-dimethylformamide (30 ml), cooled at 0°C, N,N'-dicyclohexylcarbodiimide (1.3 g, 6.4 mmol) and 1-hydroxybenzotriazole (1.04 g, 7.68 mmol) are added under stirring. After 30 minutes alendronic acid (1.6 g, 6.4 mmol) is added. The reaction mixture is left under stirring at room temperature for 7 hours. At the end it is acidified with a HCl 5% solution and the

organic phase is extracted with ethyl acetate. The organic phase is washed with brine, anhydriified with sodium sulphate and evaporated at reduced pressure. The crude product is purified by chromatography on silica gel column eluting with methylene chloride/methanol 8/2, obtaining the [4-amino-[[3-methoxy-4-(4-nitroxybutyroxyloxy)phenyl]-2-trans propenoyl]-1-hydroxy butyliden] bisphosphonic acid. Yield: 11%.

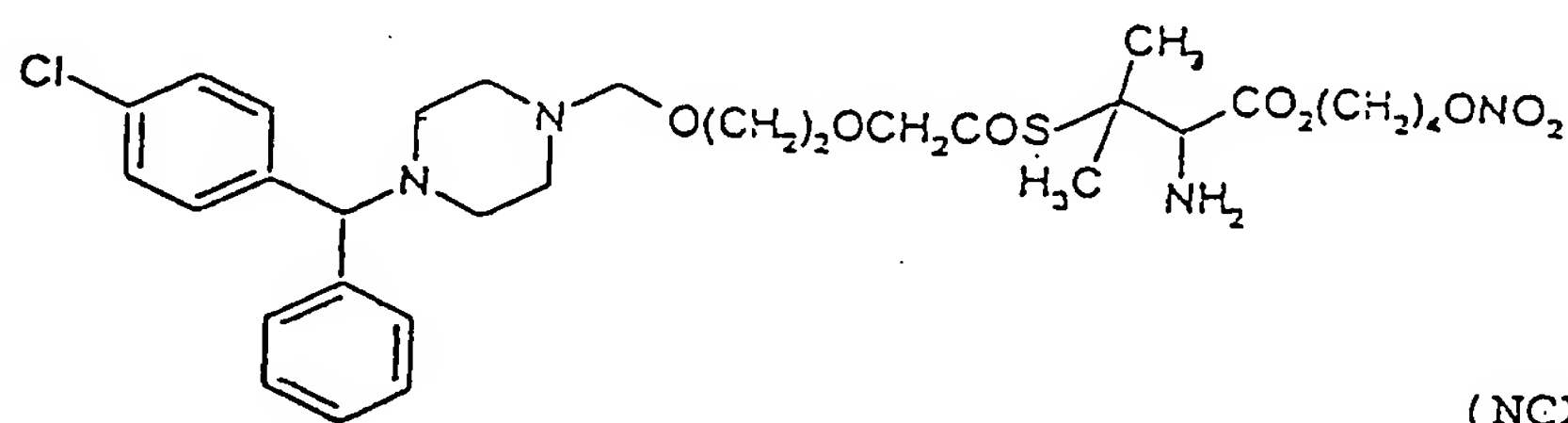
Elementary analysis:

Calculated C: 19.71% H: 4.36% N: 5.07% P: 11.17%

Found C: 19.56% H: 4.28% N: 5.04% P: 11.25%

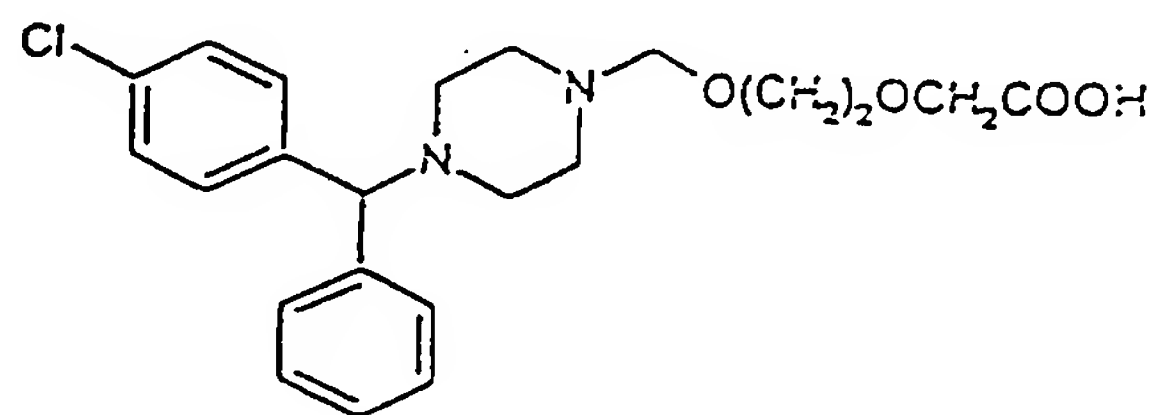
EXAMPLE 11

Preparation of S-[[2-[4-(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetyl] penicillamine 4-(nitroxy)butyl ester (NCX 2060) having formula

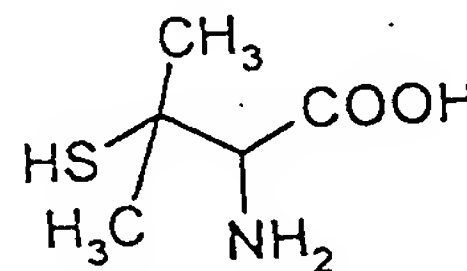


(NCX 2060)

wherein the precursor is cetirizine of formula (XIV) and the precursor of B is penicillamine (formula CV):



(XIV)



(CV)

a) Synthesis of S-[[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetyl] N-ter-butoxycarbonylpenicillamine-4-(nitroxy)butyl ester

The compound is prepared according to the procedure reported in Example 1, by using N-ter-butoxycarbonyl-penicillamine instead of N-acetyl cysteine.

b) Synthesis of S-[[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetyl]-penicillamine-4-(nitroxy)butyl ester.

The compound is obtained from the previous one by following the procedure described in step e) of Example 9 to remove the protective group N-ter-butoxycarbonyl and recover the aminic function. Yield: 26%.

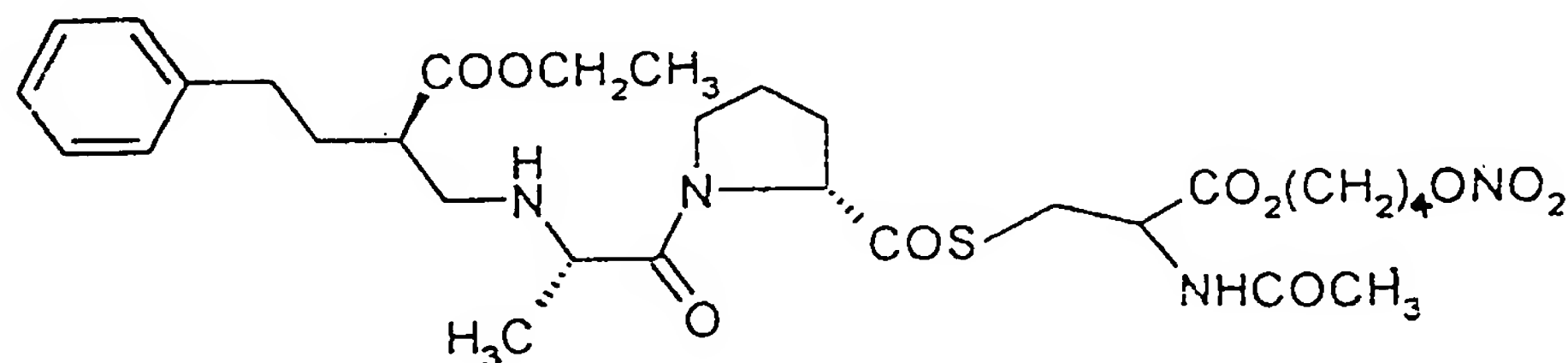
Elementary analysis:

Calculated C: 55.78% H: 6.49% N: 8.43% S: 4.80% Cl: 5.31%

Found C: 55.61% H: 6.31% N: 8.29% S: 4.93% Cl: 5.43%

EXAMPLE 12

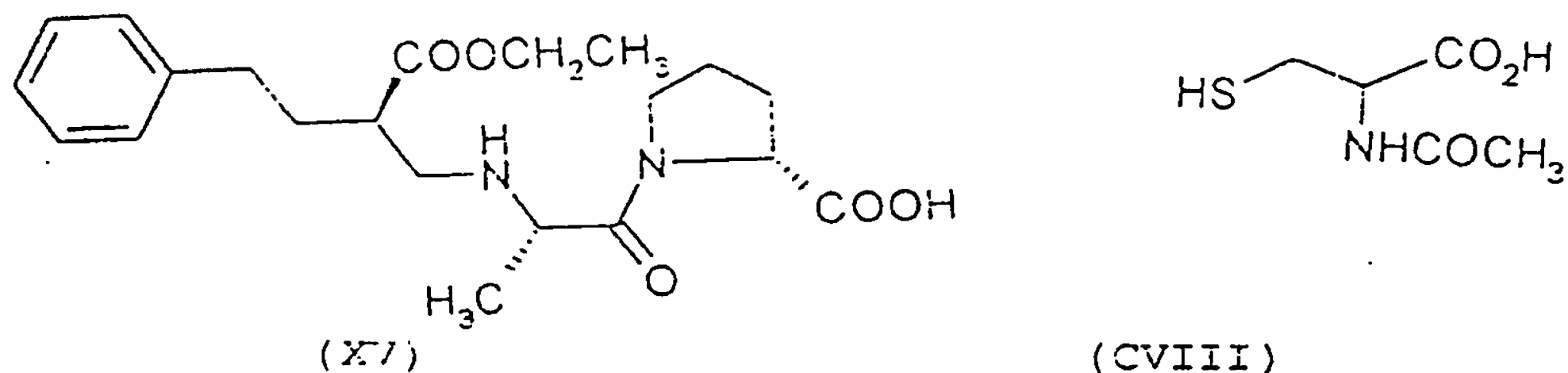
Preparation of N-acetyl-S-[(S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-prolin]cysteine 4-(nitroxy)butyl ester of formula (NCX 2134)



(NCX 2134)

wherein the precursor is enalapril of formula (XV) and the pre-

cursor of B is N-acetylcysteine (formula CVIII):



The compound is synthesized following the procedure reported in Example 1. Yield: 27%

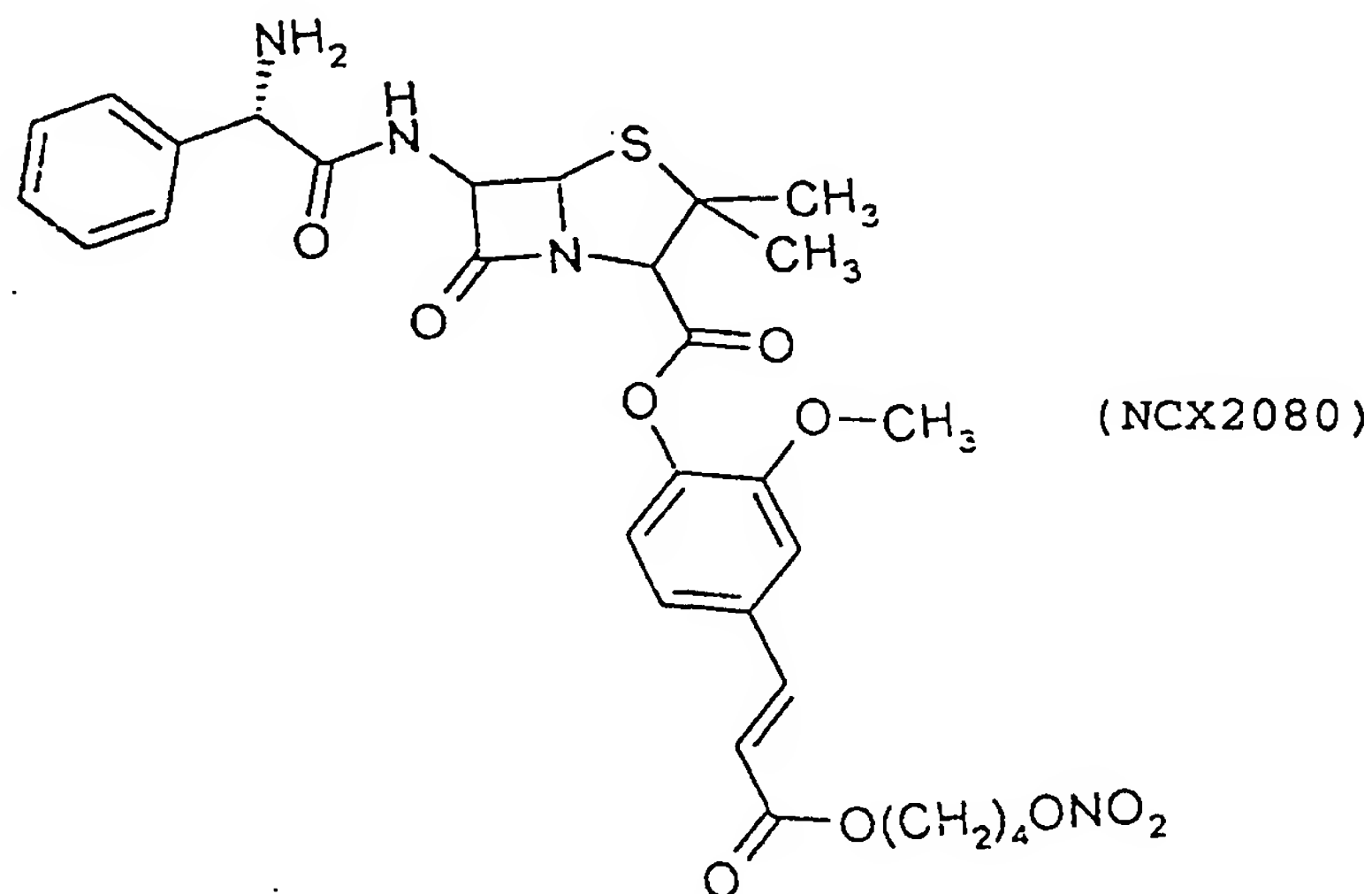
Elementary analysis:

Calculated C: 55.12% H: 6.79% N: 8.62% S: 4.91%

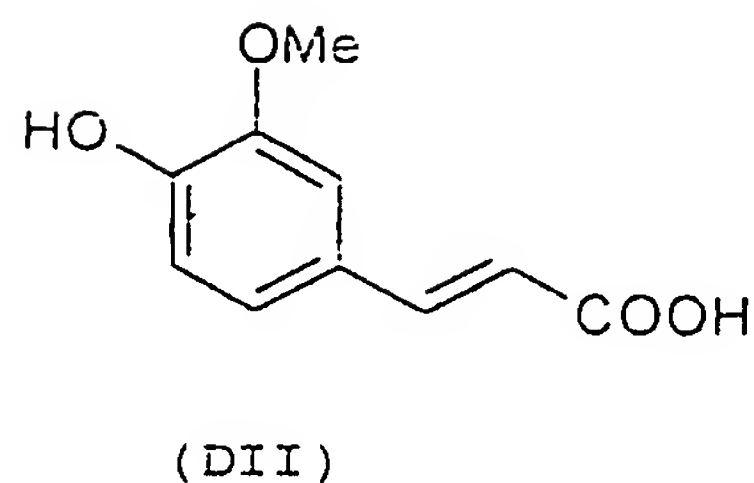
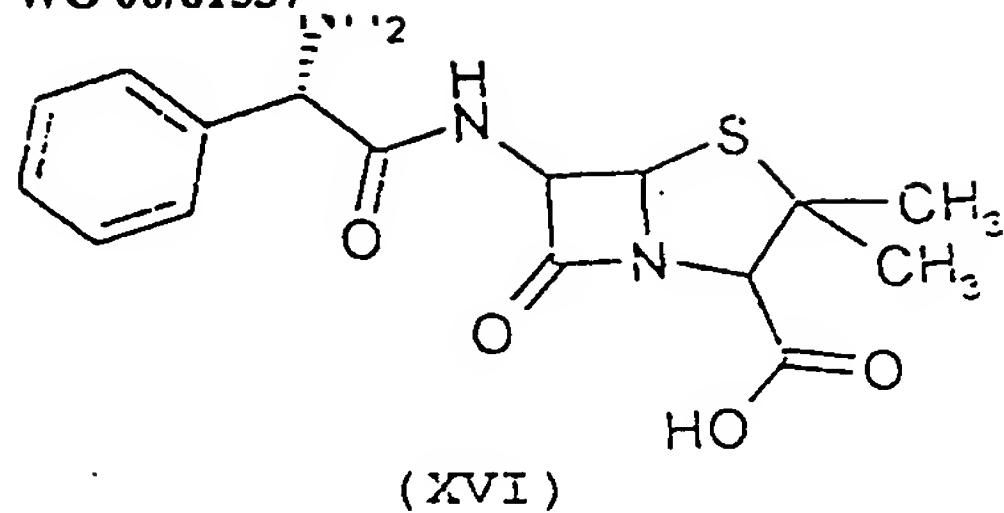
Found C: 55.30% H: 6.85% N: 8.71% S: 4.85%

EXAMPLE 13

Preparation of 3-[4-D- α -aminobenzylpenicillaminoxy]-3-methoxyphenyl-2-trans propenoyl 4-(nitroxy)butyl ester (NCX 2080) having formula



wherein the precursor is represented by ampicilline (formula XVI) and the precursor of B is ferulic acid (formula DII):



The compound is synthesized following the method reported in Example 5. Yields: 11%.

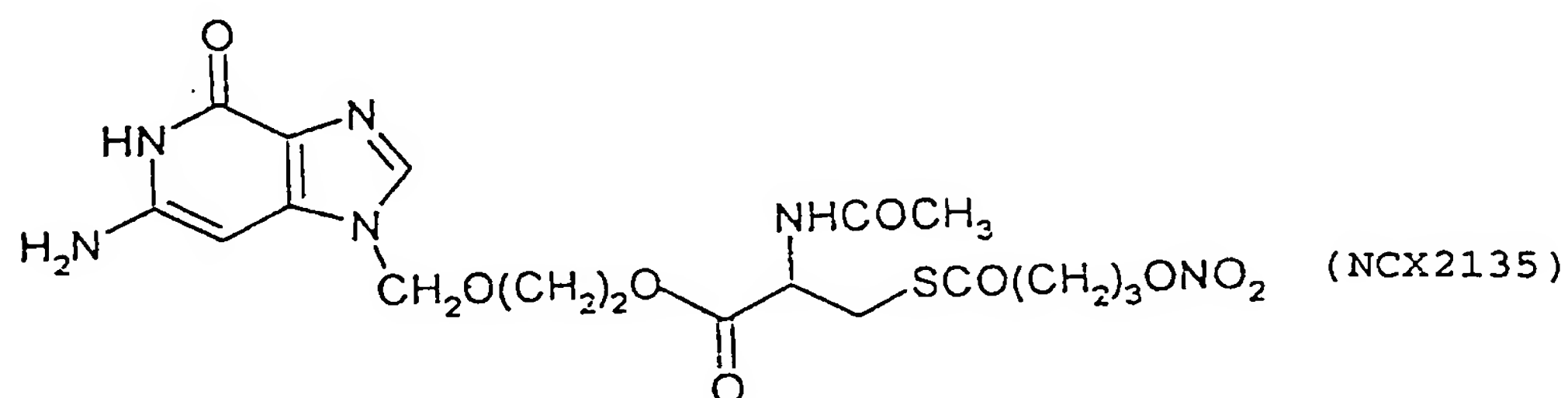
Elementary analysis

Calculated C: 56.04% H: 5.33% N: 8.75% S: 4.99%

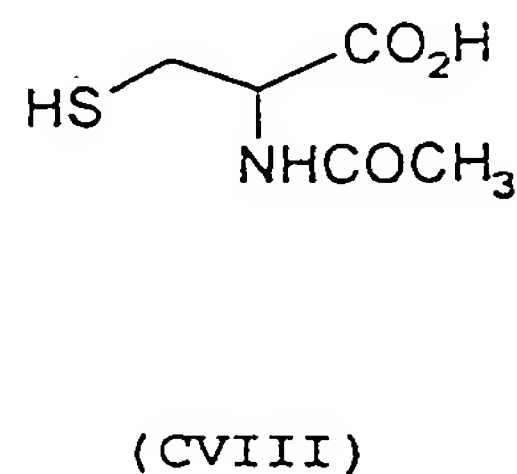
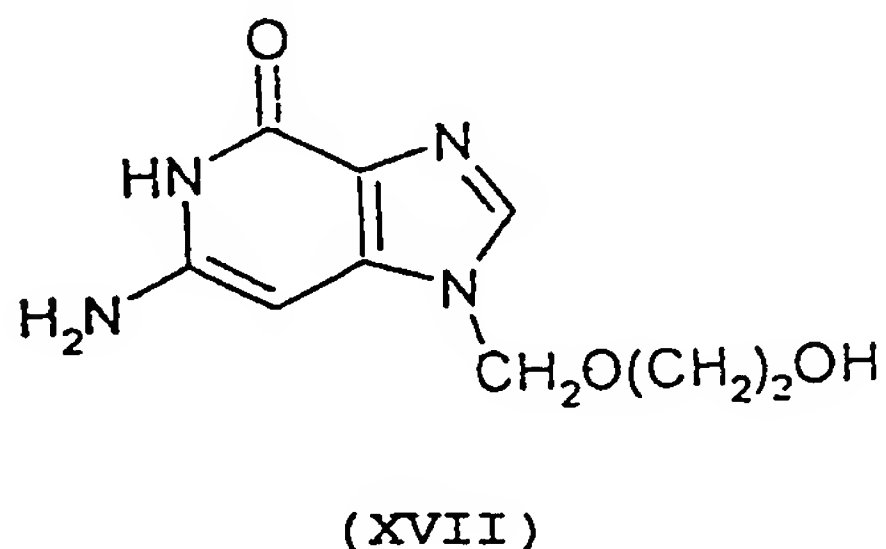
Found C: 56.15% H: 5.48% N: 8.65% S: 4.83%

EXAMPLE 14

Preparation of 9-[[2-[-N-acetyl-S-(4-nitroxybutyryl)ci-steinyl]ethoxy]-methyl]guanine of formula (NCX 2135),



wherein the precursor is aciclovir of formula (XVII) and the precursor of B is N-acetylcysteine (formula CVIII):



a) Synthesis of N-acetyl-S-(4-bromobutyroyl)cysteine

A solution containing 4-bromobutyric acid (5.1 g, 30.6 mmol) and 1,1'-carbonyldiimidazole (5.61 g, 34.6 mmol) in chloroform (50 ml) is prepared and it is left under stirring at room temperature for 1 hour. To the reaction mixture a solution of N-acetylcysteine (5 g, 30.6 mmol) in N,N-dimethylformamide (5 ml) containing sodium ethylate (50 mg) is added. It is let react under stirring and after 24 hours the solution is washed with HCl 1% and then with brine. The organic phase is anhydriified with sodium sulphate and evaporated at reduced pressure. The obtained crude product is purified by chromatography on silica gel column, eluent ethyl acetate/chloroform 7/3, lastly obtaining N-acetyl-S-(4-bromobutyroyl)cysteine.

b) Synthesis of N-acetyl-S-(4-nitroxybutyroyl)cysteine

To a solution of N-acetyl-S-(4-bromobutyroyl)cysteine (3 g, 9.6 mmol) in acetonitrile (70 ml) silver nitrate (1.7 g, 10 mmol) is added. The reaction mixture is heated under stirring under reflux for 2 hours away from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel column eluting with ethyl acetate/chloroform 7/3, lastly obtaining N-acetyl-S-(4-nitroxybutyroyl)cysteine.

c) Synthesis of 9-[[2-[N-Acetyl-S-(4-nitroxybutyroyl)cistei-

nyl]ethoxy)methyl]guanine

A solution of N-acetyl-S-(4-nitroxybutyroyl)cysteine (2.8 g, 9.6 mmol) and 1,1-carbonyldiimidazol (1.55 g, 9.6 mmol) in tetrahydrofuran (50 ml) is prepared and left under stirring at room temperature for 1 hour. The reaction mixture is treated with aciclovir (2.16 g, 9.6 mmol). After 6 hours of reaction at room temperature, the solution is evaporated at reduced pressure, the obtained residue treated with ethyl acetate and washed with brine. The organic phase is anhydriified with sodium sulphate and then dried under vacuum. The obtained residue is purified by chromatography on silica gel column eluting with ethyl acetate. 9-[[2-[N-acetyl-S-(4-nitroxybutyroyl)cisteinyl]ethoxy)methyl]guanine is obtained. Yields: 9%.

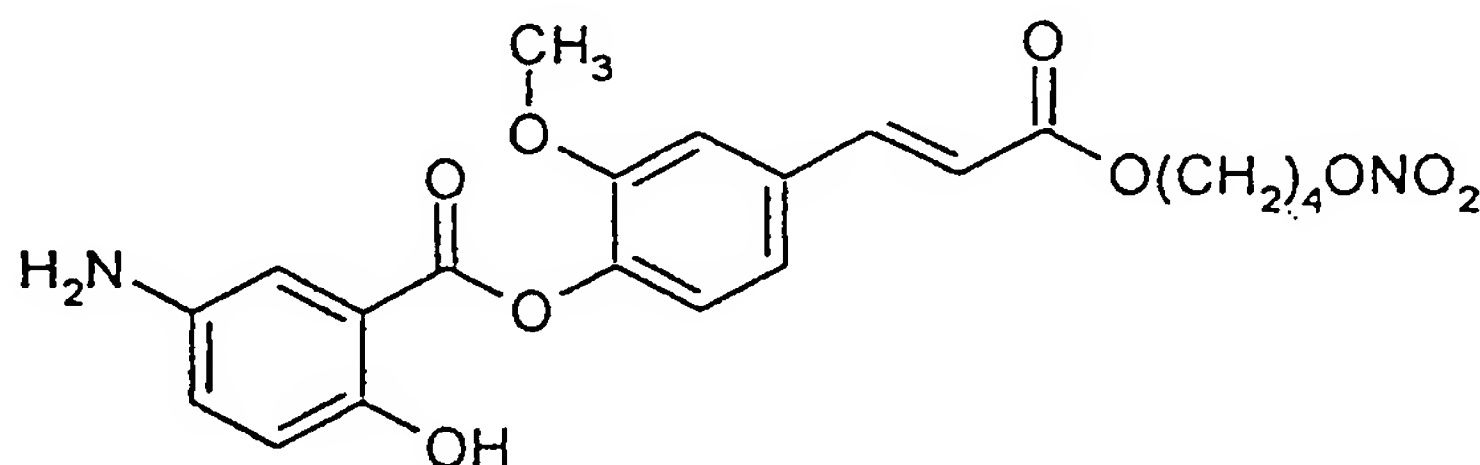
Elementary analysis

Calculated C: 35.25% H: 3.95% N: 13.76% S: 47.05%

Found C: 35.38% H: 3.99% N: 13.84% S: 47.20%

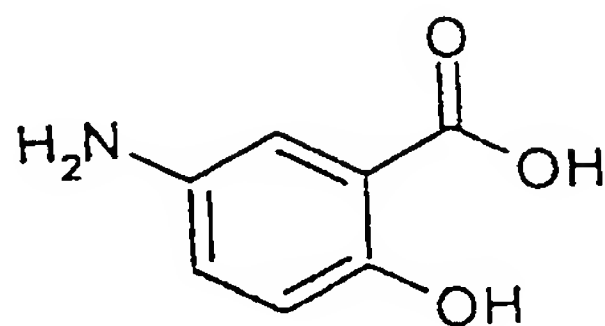
EXAMPLE 15

Preparation of trans-3-[4-(5-amino-2-hydroxybenzoyl)-3-methoxyphenyl]2-propenoyl 4-(nitroxy) butyl ester (NCX 2212),

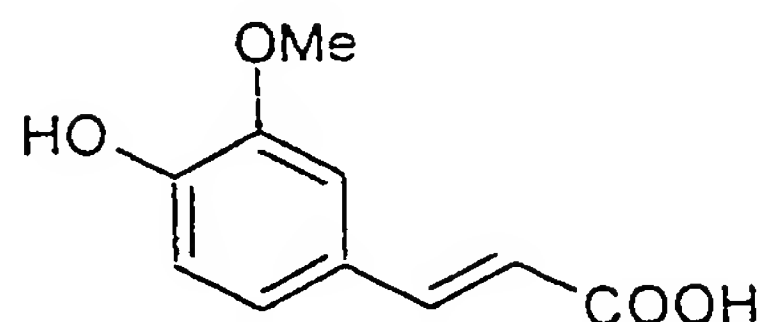


(NCX2212)

wherein the precursor is mesalamine of formula (XVIII) and the precursor of B is the ferulic acid (formula DII):



(XVIII)



(DII)

a) synthesis of trans-3-[4-(5-ter-butyloxycarbonylamino-2-hydroxybenzoyl)-3-methoxyphenyl]2-propenoic acid 4-(nitroxy)butyl ester

The compound is synthesized according to the procedure reported in Example 5, first protecting the primary aminic group of the mesalamine as described in Example 9, step a).

b) Obtaining of trans-3-[4-(5-amino-2-hydroxybenzoyl)-3-methoxyphenyl]2-propenoyl 4-(nitroxy)butyl ester

The final compound is obtained by hydrolyzing the bond between the aminic function and the N-ter-butoxycarbonyl protective group as described in Example 9, step e). Yields: 28%.

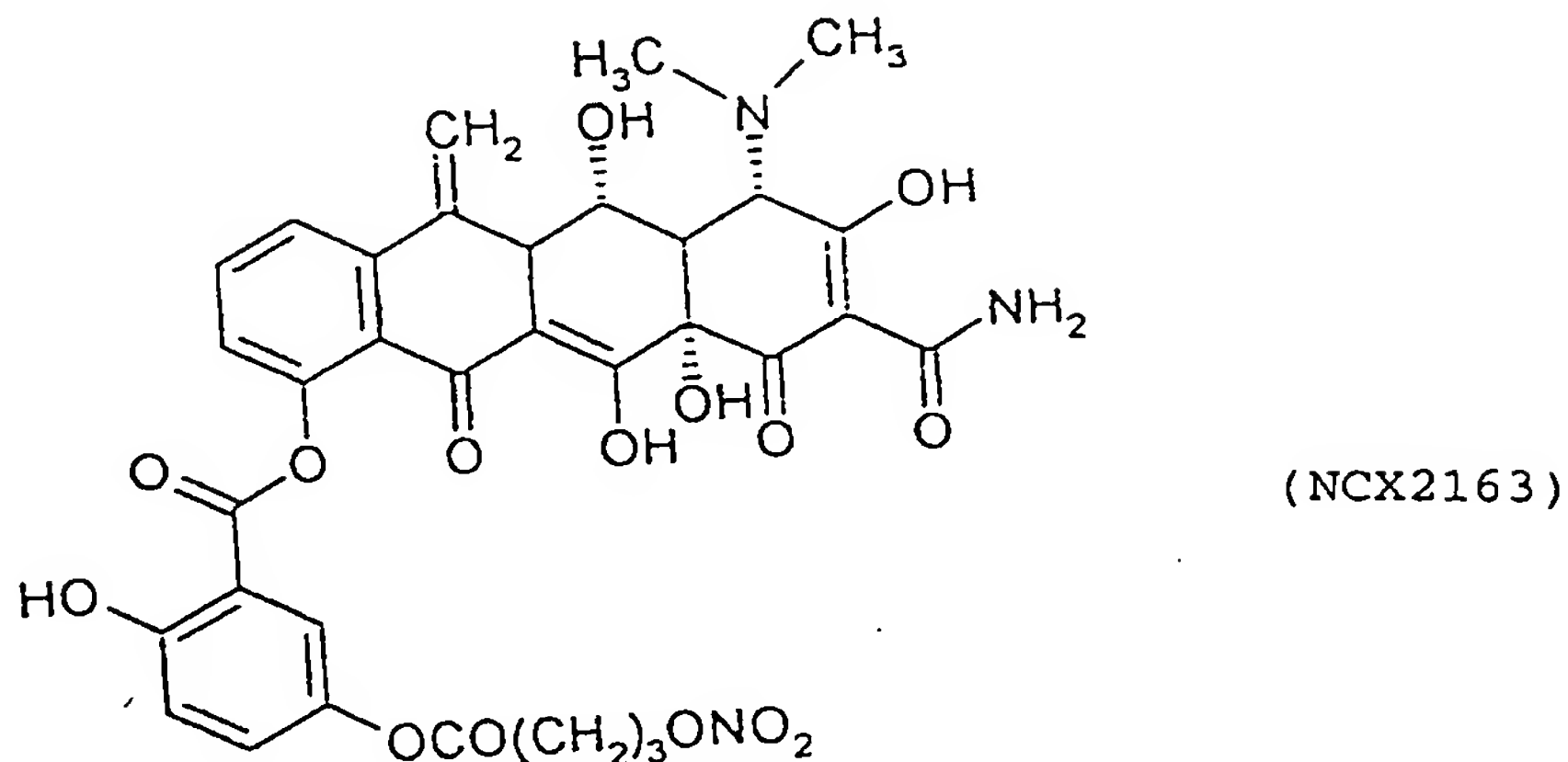
Elementary analysis:

Calculated	C: 56.49%	H: 4.96%	N: 6.30%
Found	C: 56.55%	H: 4.82%	N: 6.45%

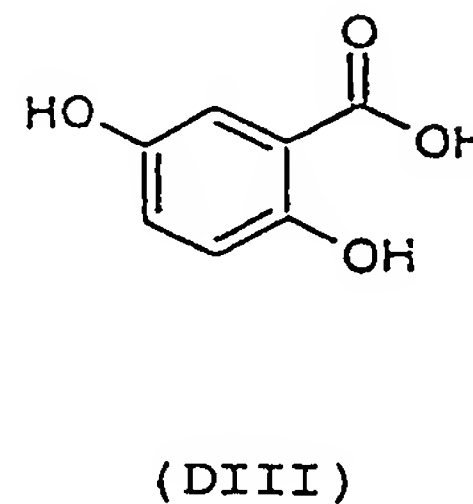
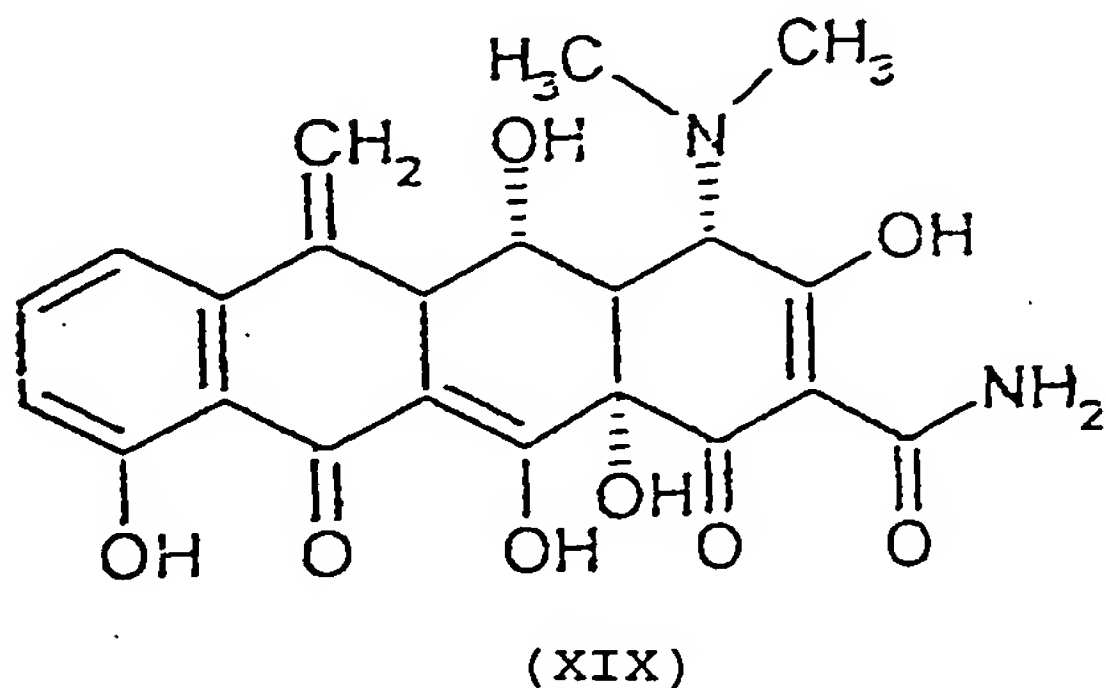
EXAMPLE 16

Preparation of 6-methylen-5-hydroxy-10[2-hydroxy-5-(4-nitro-

xybutyryloxy)benzoyl]tetracycline of formula (NCX 2163)



wherein the precursor is methacycline of formula (XIX) and the precursor of B is the gentisic acid (formula DIII):



a) Synthesis of the 5-(4-bromobutyryloxy)-2-hydroxy-benzoic acid

In a solution of 4-bromobutyrylchloride (3 g, 16.17 mmols) in tetrahydrofuran (50 ml), cooled at 0°C, triethylamine (4.5 ml, 32.34 mmols) and then gentisic acid (2.4 g, 16.16 mmoli) are dropped under stirring. It is let react at 0°C

for 4 hours, under stirring, then it is evaporated at reduced pressure. The obtained crude product is treated with ethyl acetate, the organic phase is washed with HCl 1% and then brine. The organic phase is anhydriified with sodium sulphate and dried. The obtained residue is purified by chromatography on silica gel column, eluting with methylene chloride/methanol 95/5, obtaining the 5-(4-bromobutyryloxy)-2-hydroxy-benzoic acid.

b) Synthesis of 5-(4-nitroxybutyroyloxy)-2-hydroxybenzoic acid

To a solution of 5-(4-bromobutyryloxy)-2-hydroxy-benzoic acid (3 g, 9.6 mmoles) in acetonitrile (150 ml) silver nitrate (1.7 g, 10 mmoles) is added under stirring. The mixture is heated under reflux for 7 hours away from light. Lastly the formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel column, eluting with methylene chloride/methanol 95/5. In this way the 5-(4-nitroxybutyryloxy)-2-hydroxy-benzoic acid is isolated at the pure state.

c) Synthesis of 6-methylen-5-hydroxy-10[2-hydroxy-5-(4-nitroxybutyryloxy)benzoyl]tetracycline

A solution of 5-(4-nitroxybutyryloxy)-2-hydroxy-benzoic acid (5 g, 16.4 mmoles) and 1,1'-carbonyldiimidazol (2.67 g, 16.4 mmoles) in tetrahydrofuran (70 ml) is maintained under stirring at room temperature for 1 hour. Adriamycin (7.2 g,

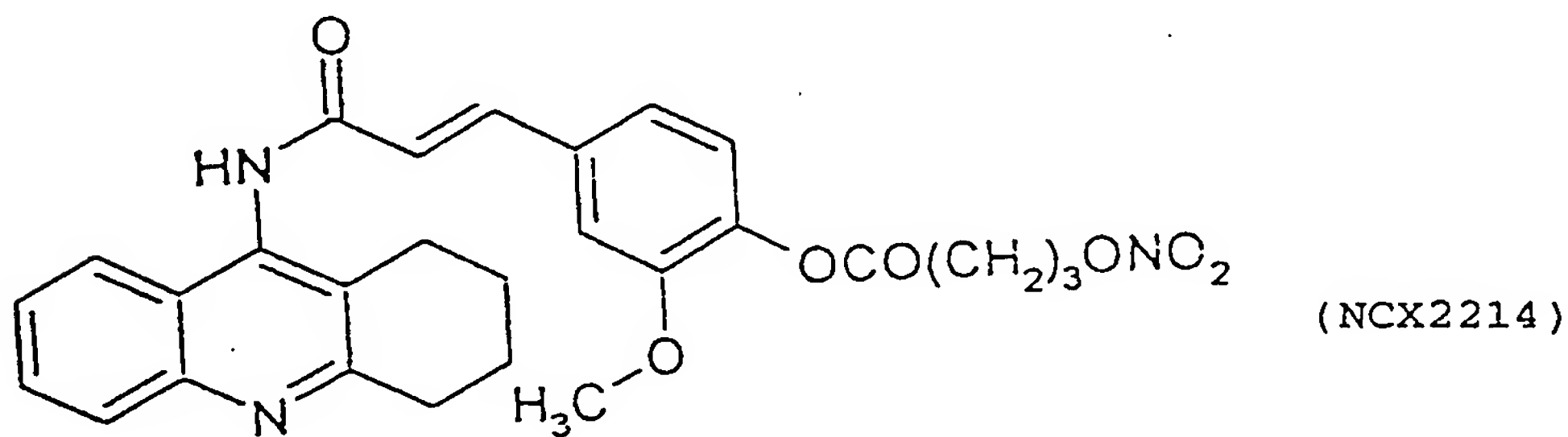
16.4 mmol) is added. It is reacted under stirring for 12 hours at room temperature. The organic solution is then evaporated at reduced pressure, the obtained residue is treated with ethyl acetate and washed with brine. The organic phase, anhydriified with sodium sulphate, is dried under vacuum. The obtained residue is purified by chromatography on silica gel column eluting with ethyl acetate. 6-methylen-5-hydroxy-10[2-hydroxy-5-(4-nitroxybutyryloxy)benzoyl]tetracycline is obtained. Yield: 19%.

Elementary analysis:

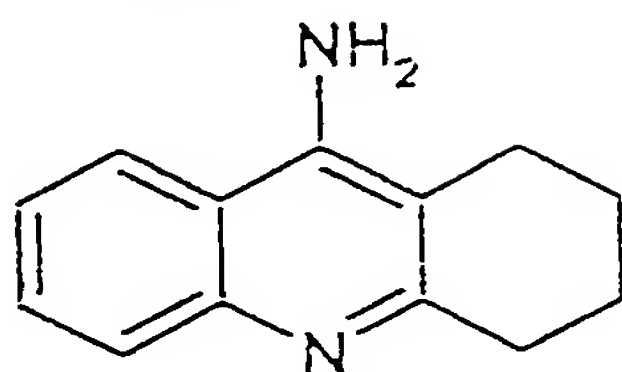
Calculated	C: 55.84%	H: 4.40%	N: 5.95%
Found	C: 55.95%	H: 4.55%	N: 5.98%

EXAMPLE 17

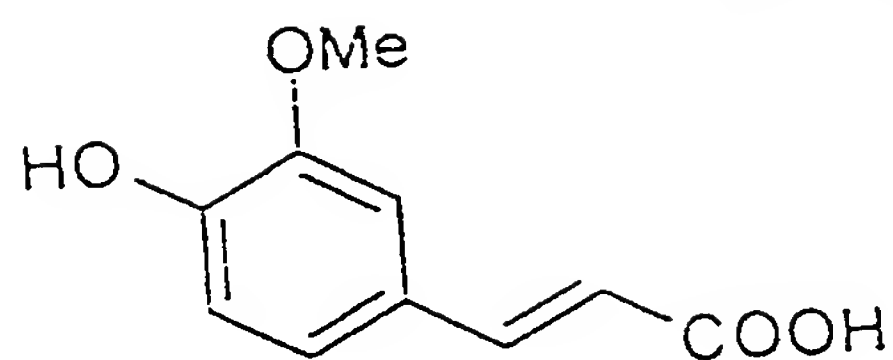
Preparation of 5-[[[3-[3-methoxy-4-(4-nitroxy)butyryloxy]phenyl]-2-trans-propenoyl]amino]-1,2,3,4-tetrahydroacridine (NCX 2214)



wherein the precursor is tacrine of formula (XX) and the precursor of B is the ferulic acid (formula DII):



(XX)



(DII)

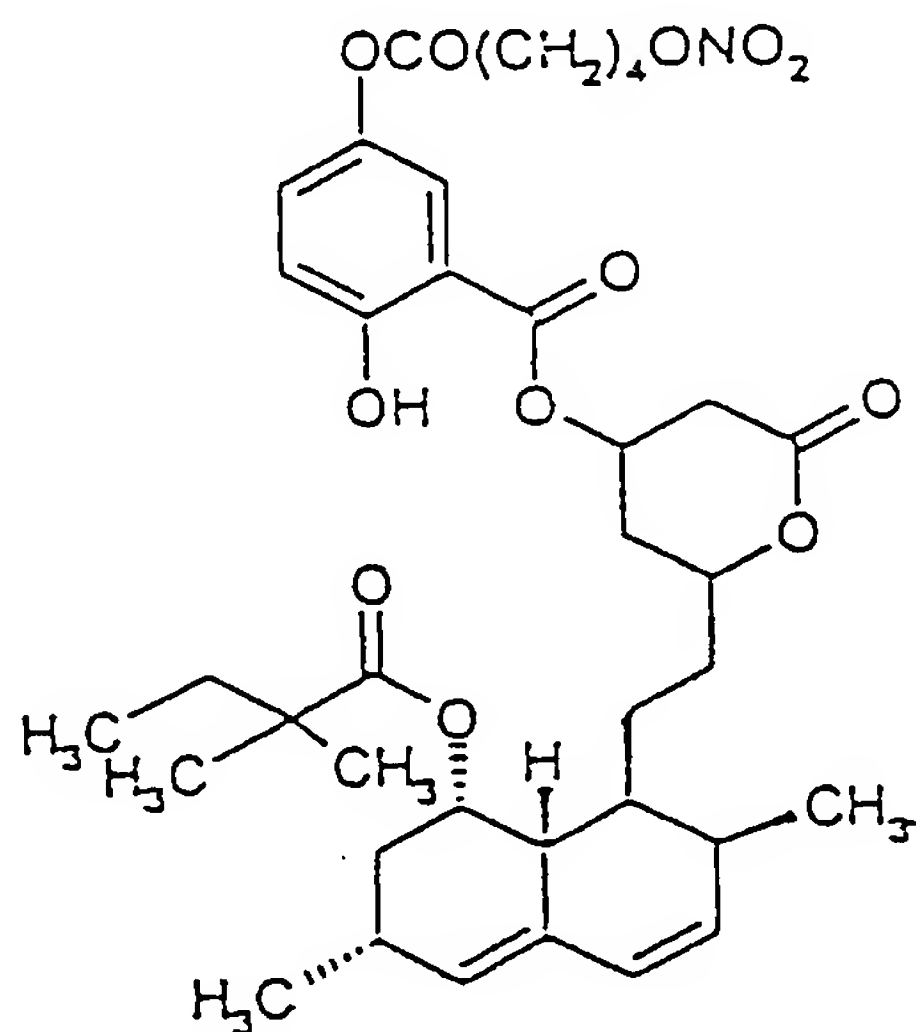
The compound is synthesized according to the procedure reported in Example 10. Yield: 7%.

Elementary analysis:

Calculated	C: 64.13%	H: 5.38%	N: 8.34%
Found	C: 64.28%	H: 5.46%	N: 8.47%

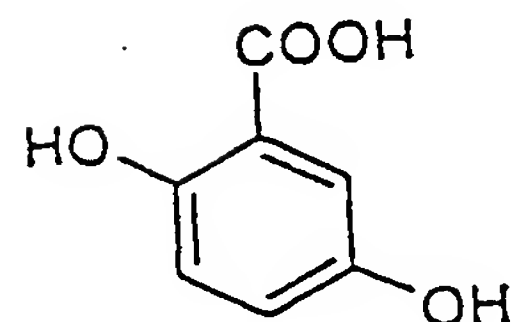
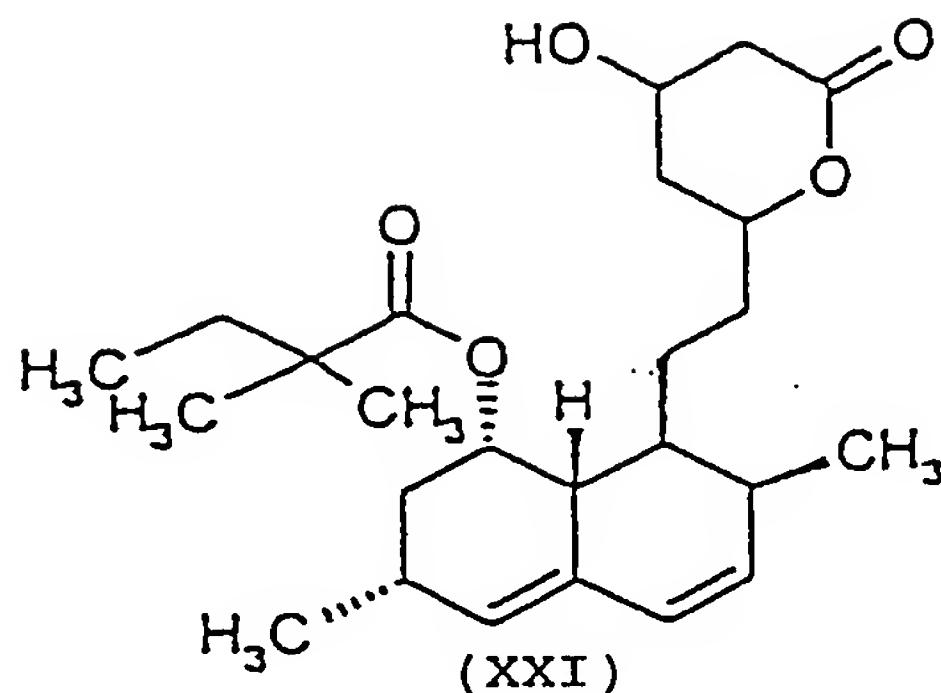
EXAMPLE 18

Preparation of [1S-[1 α ,3 α ,7 β ,8 β , (2S*,4S*)]]-2,2-dimethylbutanoic acid 1,2,3,7,8,8-hexahydro-3,7-dimethyl-8-[tetrahydro-4-[2-hydroxy-5-(4-nitroxybutyryloxy) benzoyl-oxy[-6-oxo-2H-piran-2-yl]ethyl]-1-naphthalenyl ester (NCX 2164)



(NCX2164)

wherein the precursor is simvastatine of formula (XXI) and the precursor of B is the gentisic acid (formula DIII):



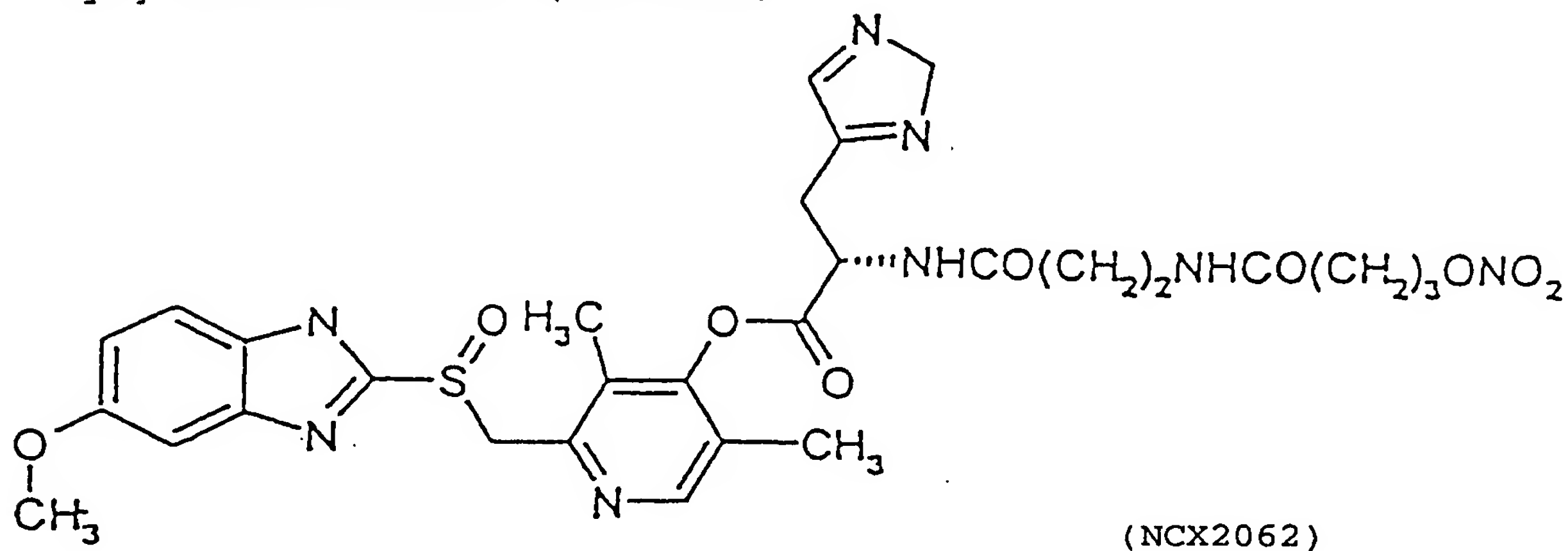
The compound is synthesized following the method described in Example 16. Yield: 13%.

Elementary analysis:

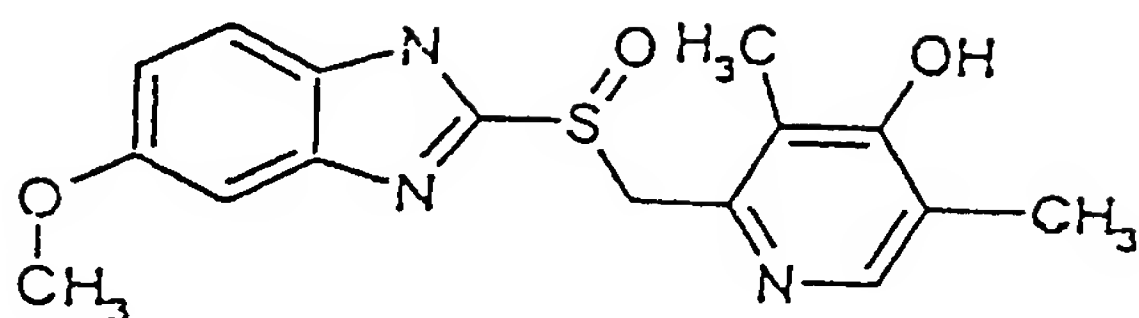
Calculated	C: 63.50%	H: 7.06%	N: 2.01%
Found	C: 63.68%	H: 7.21%	N: 2.19%

EXAMPLE 19

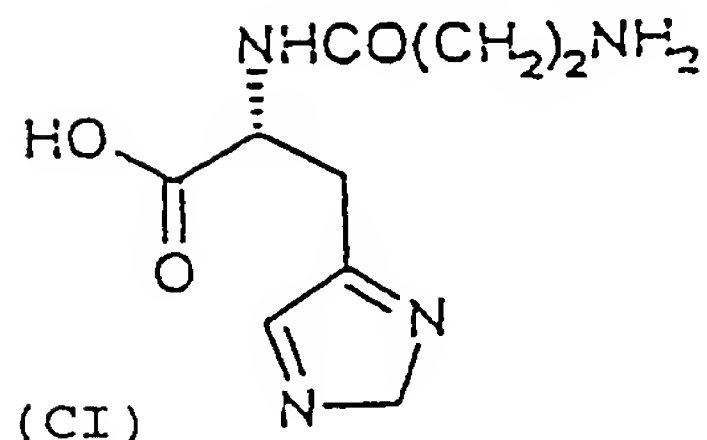
Preparation of 5-methoxy-2-[[[4-[N-[4-(nitroxy)butyl-β-alanyl](L)-histidinyloxy]-3,5-dimethyl-2-pyridinyl]methyl]sulphonyl]-1H-benzimidazol (NCX 2062)



wherein the precursor is 4-hydroxyomeprazol of formula (XXII), obtained by treating omeprazol as described in Acta Chem. Scand. 43, 6 1989 pages 549-568 and the precursor of B is carnosine (formula CI):



(XXII)



(CI)

The compound is synthesized according to the process described in Example 7. Yield: 25%

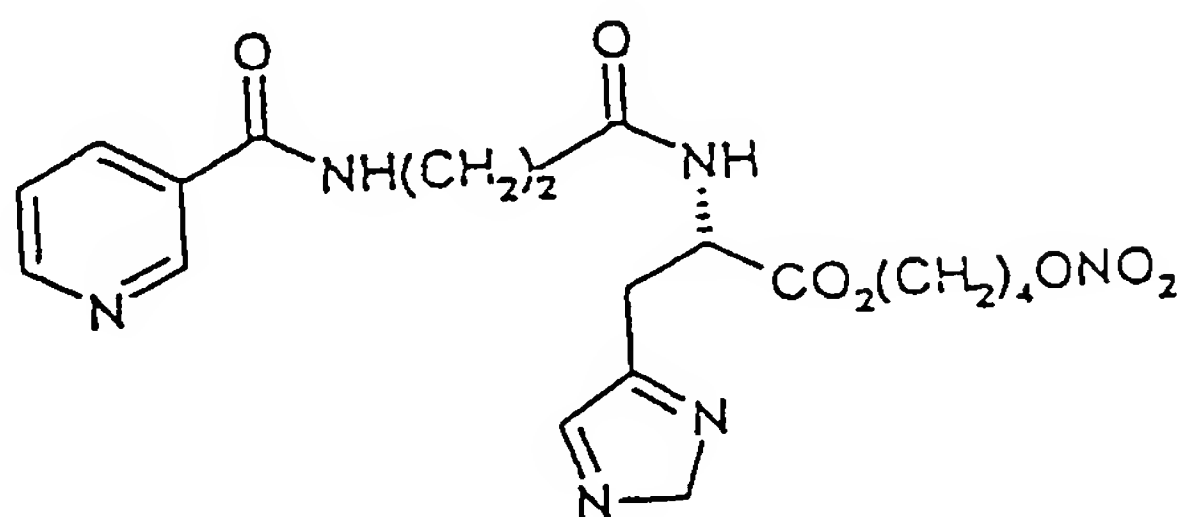
Elementary analysis:

Calculated C: 51.97% H: 4.96% N: 16.79% S: 4.78%

Found C: 51.81% H: 4.80% N: 16.68% S: 4.92%

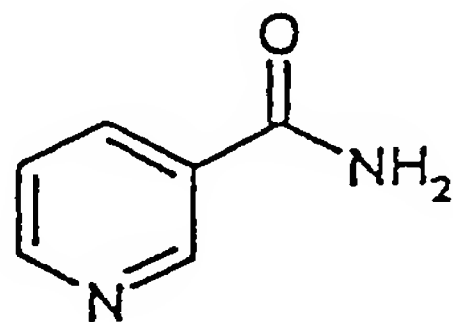
EXAMPLE 20

Preparation of N-nicotinoyl- β -alanyl (L)-histidine 4-(nitroxy)butyl ester (NCX 2073)

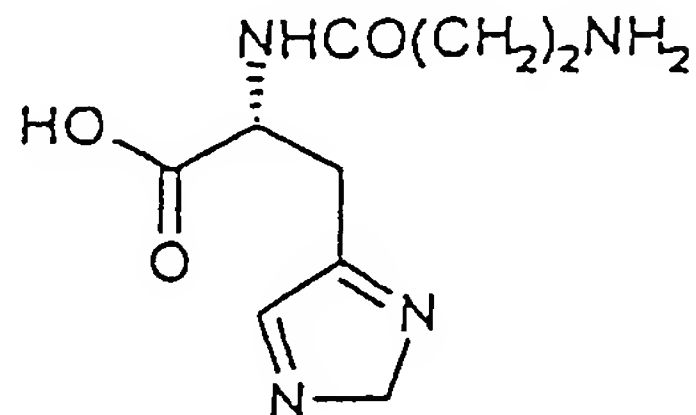


(NCX2073)

wherein the precursor is nicotinamide of formula (XXIII) and the precursor of B is carnosine (formula CI):



(XXIII)



(CI)

a) Synthesis of N-nicotinoyl- β -alanyl (L)-histidine

To a solution of nicotinic acid (2.5 g, 20.5 mmol) in tetrahydrofuran (40 ml) cooled at 0°C, 1,1'-carbonyldiimidazol (3.34 g, 20.5 mmol) is added under stirring. After 10 minutes to the solution (L)-carnosine (4.6 g, 20.5 mmol) is added and it is left under stirring at room temperature for 4 hours. The reaction mixture is concentrated under vacuum, treated with methylene chloride, washed with HCl 1% and then with water. The organic phase is anhydriified with sodium sulphate and evaporated under vacuum. The obtained residue is chromatographed on silica gel column, eluting with ethyl acetate. N-nicotinoyl- β -alanyl (L)-histidine is recovered.

b) Synthesis of N-nicotinoyl- β -alanyl (L)-histidine 4-bromobutyl ester

To a solution of N-nicotinoyl- β -alanyl-(L)-histidine (9.9 g, 30.1 mmol) in tetrahydrofuran (200 ml) triphenylphosphine (23.7 g, 90.3 mmol) and carbon tetrabromide (28.85 g, 90.3 mmol) are added under stirring. The reaction mixture is left under stirring at room temperature for 24 hours. Lastly the solvent is removed by evaporation at reduced pressure. The obtained crude product is purified by chromatography on silica gel column eluting with n-hexane/ethyl acetate 1/1. N-nicotinoyl- β -alanyl-(L)-histidine 4-bromobutyl ester is obtained.

c) Synthesis of N-nicotinoyl- β -alanyl (L)-histidine 4-nitroxybutyl ester

To a solution of N-nicotinoyl- β -alanyl (L)-histidine 4-bromobutyl ester (0.91 g, 1.96 mmol) in acetonitrile (20 ml) silver nitrate (0.66 g, 3.92 mmol) is added under stirring. The reaction mixture is heated to reflux under stirring for 4 hours away from light. Lastly the formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel column eluting with n-hexane/ethyl acetate 1/1. N-nicotinoyl- β -alanyl-(L)-histidine 4-nitroxybutyl ester is obtained. Yields: 32%.

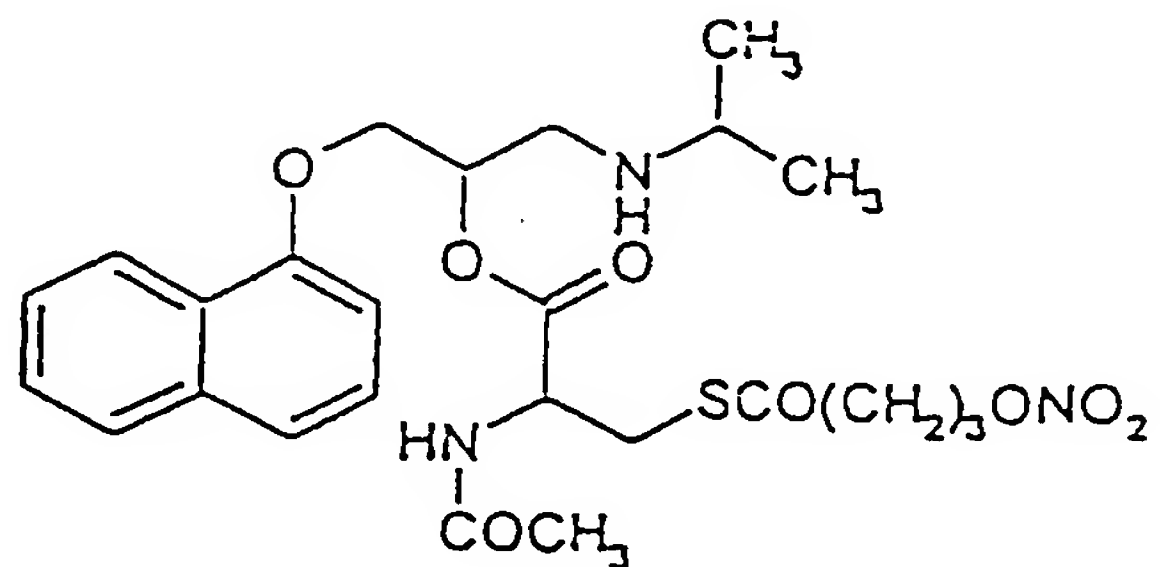
Elementary analysis:

Calculated C: 49.50% H: 5.54% N: 19.32%

Found C: 49.35% H: 5.28% N: 19.17%

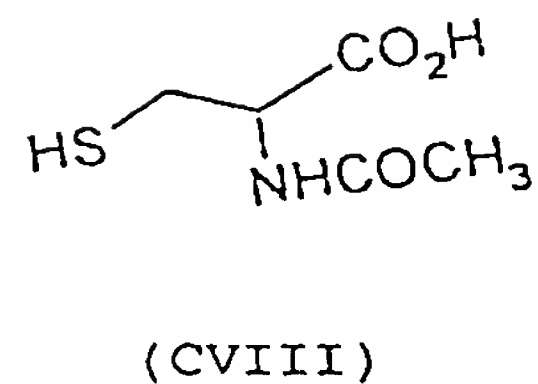
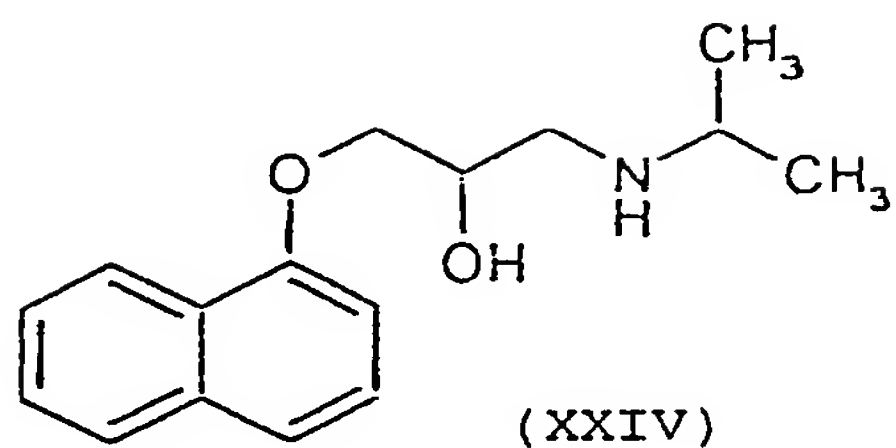
EXAMPLE 21

Preparation of N-acetyl-S-(4-nitroxybutyryl) cysteine 1-[(1-methylethyl) amino]-3-(1-naphthalen oxy)-2-propanol ester (NCX 2132)



(NCX2132)

wherein the precursor is propranolol of formula (XXIV) and the precursor of B is N-acetylcysteine (formula CVIII):



The compound is synthesized with the process described in Example 14. Yields: 7%.

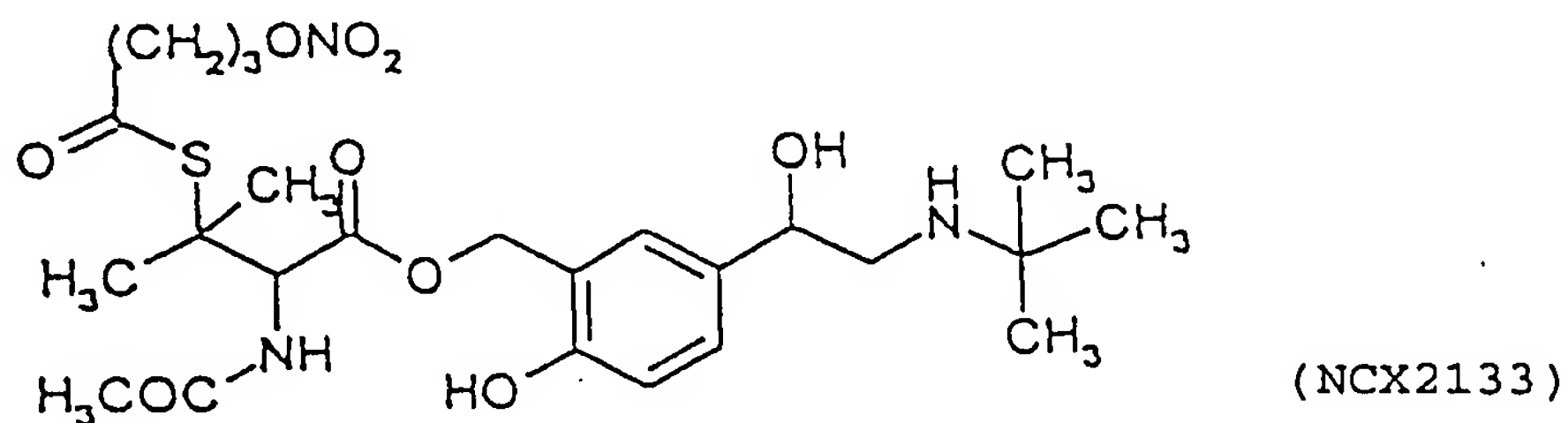
Elementary analysis:

Calculated C: 56.04% H: 6.21% N: 7.88% S: 5.98%

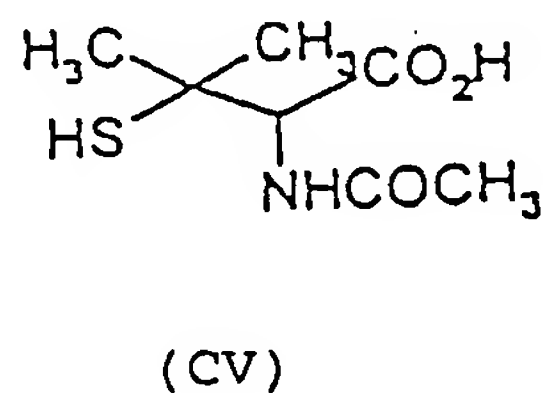
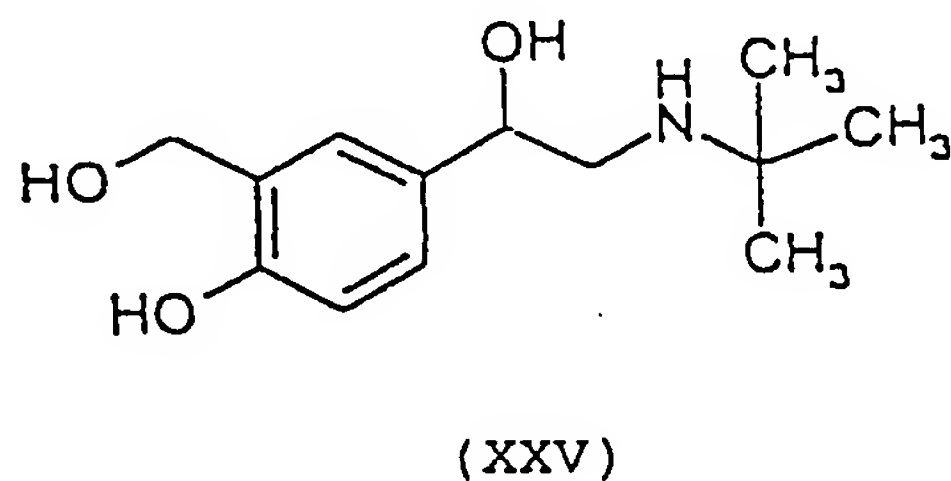
Found C: 56.13% H: 6.35% N: 7.91% S: 6.04%

EXAMPLE 22

Preparation of 2-(ter-butylamino)-1-[4-hydroxy-3-[N-acetyl-S-(4-nitroxybutyryl)-penicillaminoyl]oxyphenyl]ethanol (NCX 2133)



wherein the precursor is salbutamol (albuterol) of formula (XXV) and the precursor of B is N-acetylpenicillamine (formula CV):



The compound is synthesized by following the procedure reported in Example 14, using N-acetyl penicillamine instead of N-acetylcysteine. Yields: 43%

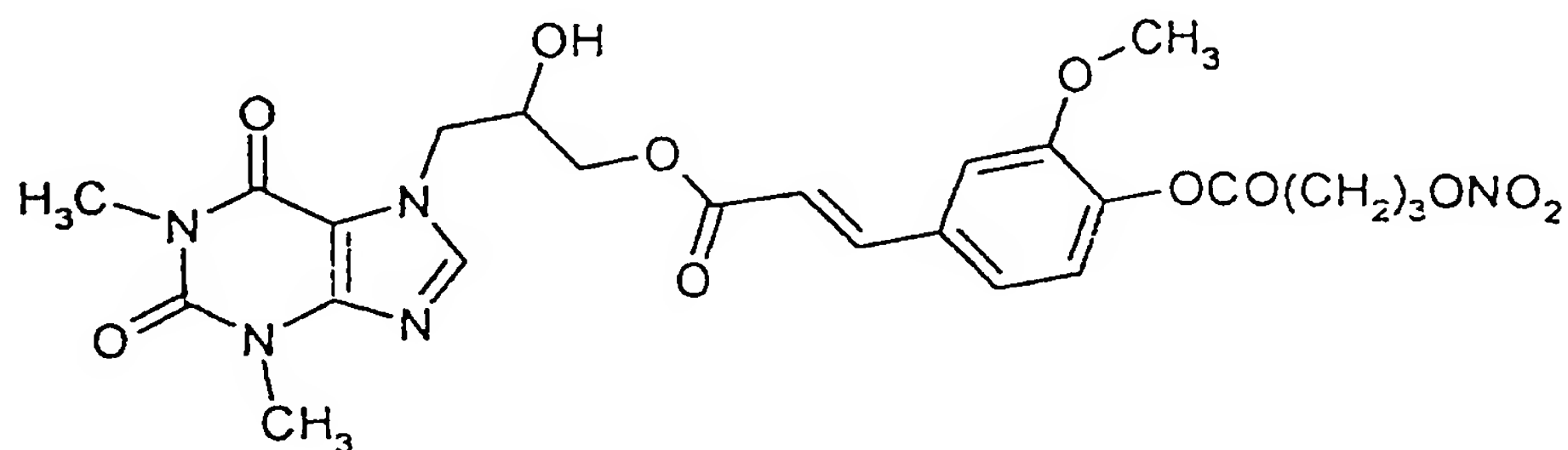
Elementary analysis:

Calculated C: 53.01% H: 6.86% N: 7.76% S: 5.89%

Found C: 53.19% H: 6.80% N: 7.66% S: 5.72%

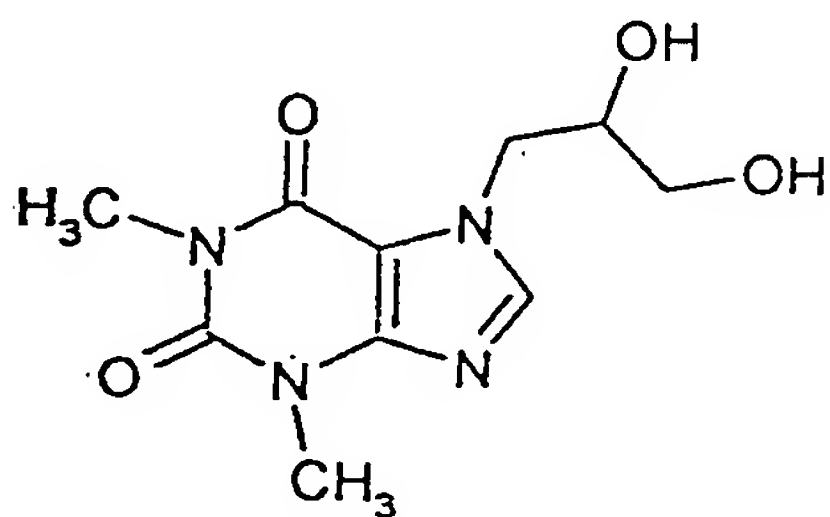
EXAMPLE 23

Preparation of 7-[2-hydroxy-3-[3-methoxy-5-(4-nitrooxybutyryloxy)benzoyl] trans-2-propenoyl]theophylline (NCX 2213)

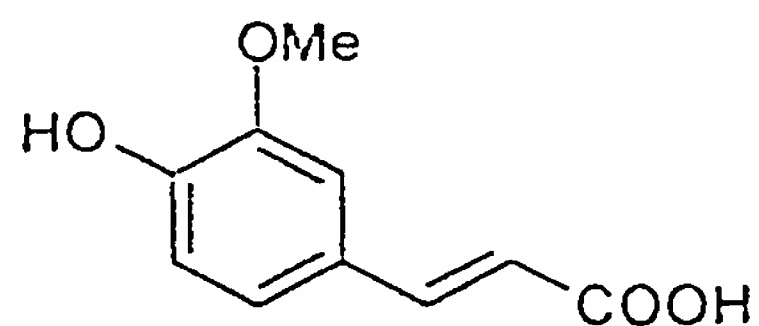


(NCX2213)

wherein the precursor is the diphylline of formula (XXVI) and the precursor of B is the ferulic acid (formula DII):



(XXVI)



(DII)

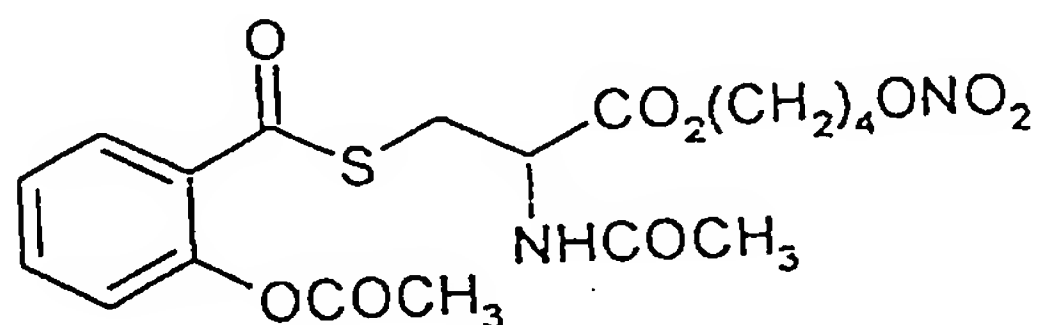
The drug is synthesized according to the process described in Example 9. Yield: 22%

Elementary analysis:

Calculated	C: 51.31%	H: 4.84%	N: 12.52%
Found	C: 51.50%	H: 4.91%	N: 12.68%

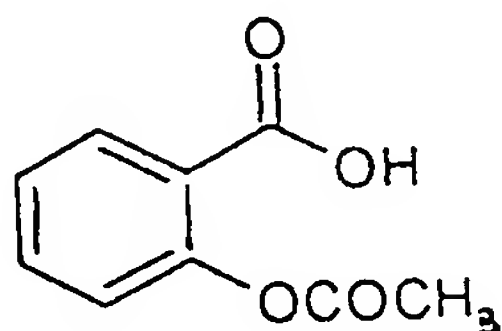
EXAMPLE 24

Preparation of N-acetyl-S-(2-acetylbenzoyl)cysteine 4-(nitroxy)butyl ester (NCX2138) of formula

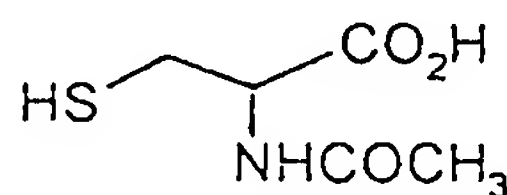


(NCX2138)

wherein the precursor is acetylsalicylic acid of formula (XXVII) and the precursor of B is N-acetylcysteine (formula CVIII-I):



(XXVII)



(CVIII)

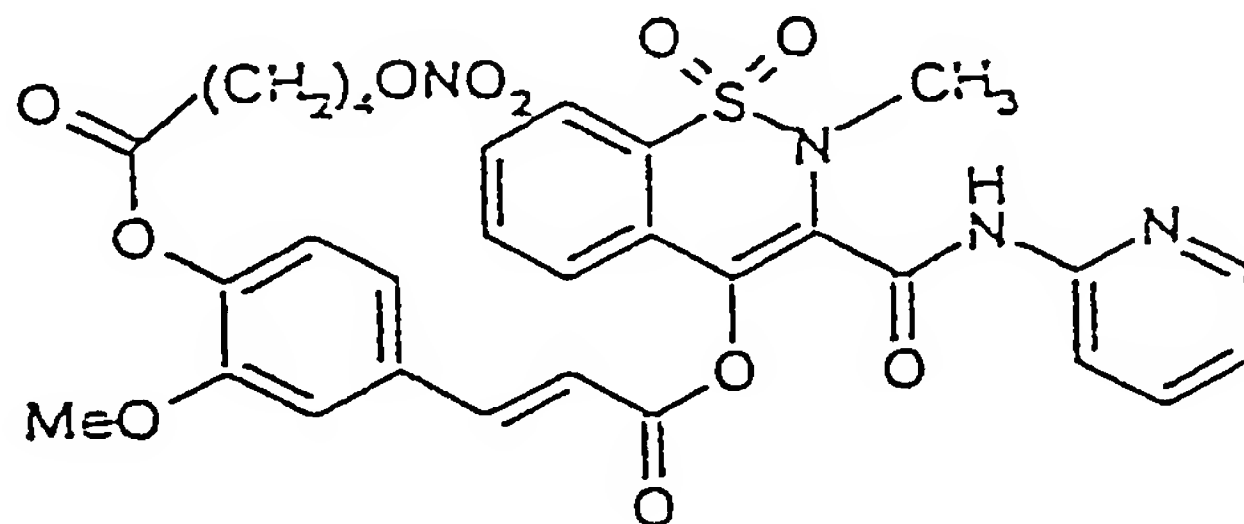
The compound is synthesized according to the process described in Example 1. Yield 36%.

Elementary analysis

Calculated	C: 48.85%	H: 5.01%	N: 6.36%	S: 7.24%
Found	C: 48.75%	H: 5.02%	N: 6.28%	S: 7.12%

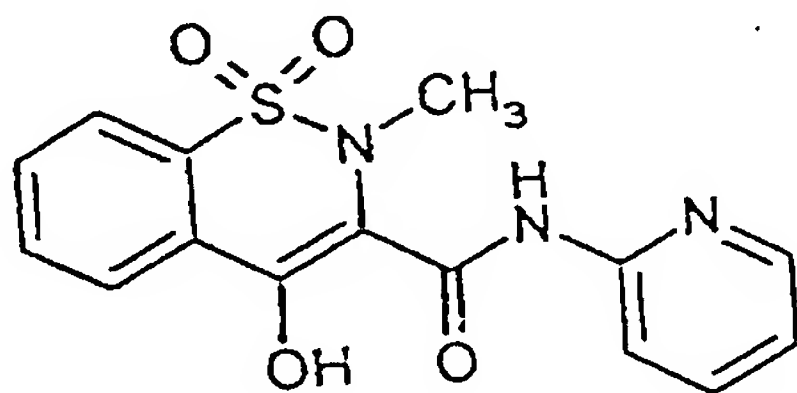
EXAMPLE 25

Preparation of 4-[3-[3-methoxy-5-(4-nitroxybutyryloxy)phenyl]-2-propenoyloxy]-2-methyl-N-2-pyridinyl-2H-1,2-benzothiazin-3-carboxamide-1,1-dioxide (NCX2215)

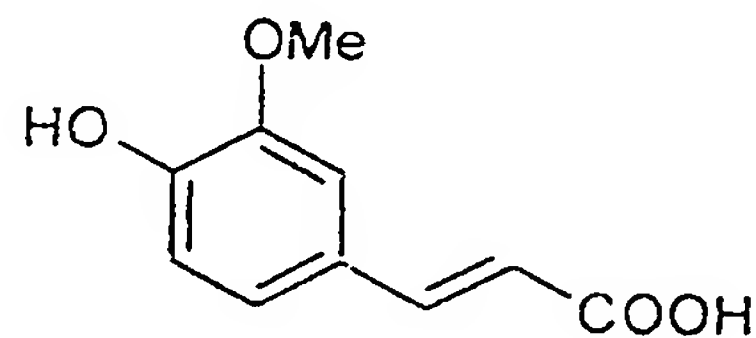


(NCX2215)

wherein the precursor is piroxicam of formula (XXVIII) and the precursor of B is ferulic acid (formula DII):



(XXVIII)



(DII)

The compound is synthesized according to the process reported in Example 9. Yield 18%.

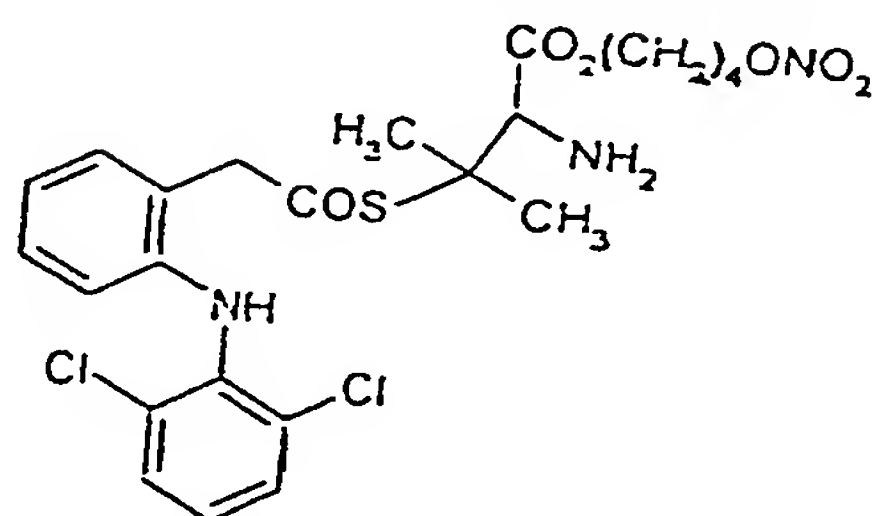
Elementary analysis

Calculated	C: 55.11%	H: 4.47%	N: 8.60%	S: 4.90%
Found	C: 55.18%	H: 4.52%	N: 8.71%	S: 4.98%

EXAMPLE 26

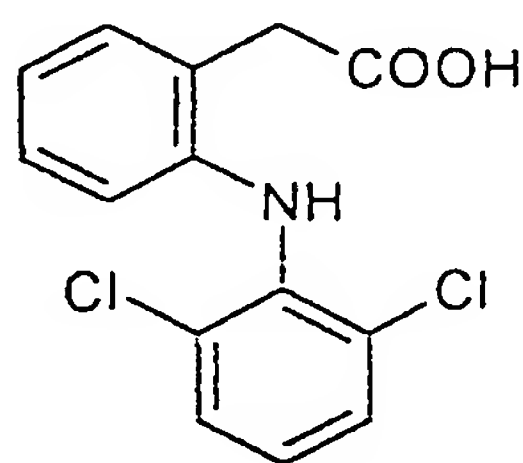
Preparation of S-[2-[(2,6-dichlorophenyl)amino]benzeneaceti-

loxy]penicillamine 4-(nitroxy)butyl ester (NCX 2061) of formula

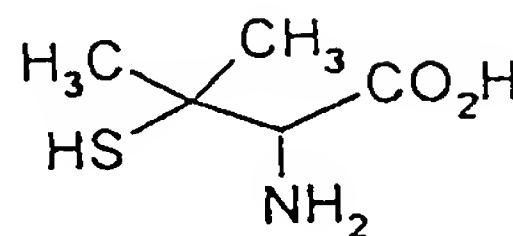


(NCX2061)

wherein the precursor is diclofenac of formula (XXIX) and the precursor of B is penicillamine (formula CV):



(XXIX)



(CV)

The compound is synthesized according to the process described in Example 11. Yield 21%.

Elementary analysis

Calculated C: 50.72% H: 5.00% N: 7.75% S: 5.89% Cl: 13.02%

Found C: 50.61% H: 4.89% N: 7.81% S: 6.01% Cl: 13.21%

PHARMACOLOGICAL TESTS

EXAMPLE

Acute Toxicity

Acute toxicity has been evaluated by administering to a group of 10 rats weighing 20 g a single dose of each of the tested compounds, by cannula, by os in an aqueous suspension of carboxymethylcellulose 2% w/v.

The animals are kept under observation for 14 days. In no animal of the group toxic symptoms appeared, even after administration of a 100 mg/Kg dose.

EXAMPLE F1

Test 1 - experimental model in vivo with N-ethylmaleimide (NEM): study of the gastric tolerability of some drugs screened as precursors of the compounds of the invention.

The animals (rats, weight about 200 g) are distributed in the following groups (No. 10 animals for group):

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, physiologic solution when by parenteral route),

2° group: treatment: carrier + NEM,

B) Groups administered with each drug:

group I: treatment: carrier + drug,

group II: treatment: carrier + drug + NEM.

The drugs assayed in this experiment are the following (Table I): indomethacin, ambroxol, mesalamine, sodic alendronate, tacrine, omeprazol, misoprostol.

Indomethacin, ambroxol and alendronate are administered by os, mesalamine by intracolonic (rectal) route and tacrine, omeprazol, misoprostol by subcutaneous route.

The maximum tolerated dose, determined by administering

each substance by the above said routes to the animals not treated with NEM, is reported in Table I. With higher doses than those reported in the Table, enteropathy, diarrhoea, depression, tremor and sedation have appeared in the animals.

In this experimental model the animals are at first treated with NEM by subcutaneous injection at a dose of 25 mg/kg in physiologic solution. The drug is administered one hour later, in suspension in the carrier. Animals are sacrificed after 24 hours and evaluation of the damage to the gastrointestinal mucosa is made by counting the number of rats, inside each group, with lesions to the stomach at a visual inspection. The total number of said rats is then divided by the total number of rats of the group and multiplied by 100. The thus obtained percentages are reported in Table I. The Table shows that in the groups of rats treated with said drugs without NEM, no gastric lesions were detectable.

All the rats of group II (treated with NEM) showed gastric lesions after administration with the following drugs: indomethacin, ambroxol, mesalamine, sodic alendronate, tacrine. Said drugs therefore can be used in the synthesis of the products of the invention.

Omeprazol and misoprostol cannot instead be used, on the basis of the results provided in test 1, for preparing the products of the invention.

EXAMPLE F2

Test 2 (in vitro): inhibition of apoptosis (DNA fragmentation) induced in the endothelial cells by CIP in the presence of some drugs screened as precursors of the compounds of the invention.

The following precursor drugs (Table II): indomethacin, paracetamol, clopidogrel, salbutamol, ambroxol, sodic alendronate, dipylline, cetirizine, enalapril, nicotinamide, ampicilline, aciclovir, mesalamine, tacrine, simvastine, omeprazol have been tested.

Human endothelial cells of the umbilical vein are prepared according to a standard method. Fresh umbilical veins are filled with a collagenase solution 0.1% by weight and incubated at 37°C for 5 minutes.

Subsequently the veins are perfused with the medium M 199 (GIBCO, Grand Island, NY) pH 7.4 with 0.1% (weight/volume) of collagenase, added with 10% of bovine fetus serum (10 mcg/ml), sodium heparin (50 mcg/ml), thimidine (2.4 mcg/ml), glutamine (230 mcg/ml), penicillin (100 UI/ml), streptomycin (100 mcg/ml) and streptomycin B (0.125 mcg/ml). The cells are collected from the perfusate by centrifugation at 800 rpm and harvested in culture flasks T-75, pretreated with human fibronectin. Cells are then harvested in the same medium, added with bovine hypothalamic growth factor (100 ng/ml). When the cells of the primary cell culture (the cells directly removed from ex-vivo umbilical vein) form a single layer of

confluent cells (about 8,000,000 cells/flask), harvesting is stopped and the layers are washed and trypsinized. The cellular suspensions are transferred into wells of a culture plate having 24 wells, half of said wells being added with the same culture medium containing the drug at a 10^{-4} M concentration, and harvested in a thermostat at 37°C at a constant moisture (90%), $\text{CO}_2 = 5\%$. When the drug is not soluble in the culture medium, it is formerly dissolved in a small amount of dimethylsulphoxide. The maximum amount of dimethylsulphoxide which can be added to the culture medium is 0.5%. Only the cells coming from these first subcultures are used for the tests with cumene hydroperoxide (CIP). The cells are identified as endothelial cells by morphological examination and by the specific immunological reaction towards factor VIII; these cultures did never show contaminations from myocytes or fibroblasts.

Before starting the test, the cellular culture medium is removed and the cellular layers are carefully washed with a standard physiologic solution buffered with phosphate 0.1 M pH 7.0, at the temperature of 37°C. The content of each well is then incubated for one hour with a CIP suspension in the culture medium at a 5 mM concentration. Evaluation of the cellular damage (apoptosis) is carried out by determining the per cent variation of the DNA fragmentation in the cultures containing the drug + CIP with respect to the controls treated

with CIP only. Said % variation of DNA fragmentation is determined by evaluating the fluorescence variation by a BX60 Olympus microscope (Olympus Co., Roma) set at the wave length of 405-450 nm, of the test samples with respect to the optical density of the controls. The fluorescence of each sample was determined on 5 replicates. Statistic evaluation has been made with t Student test ($p < 0.01$).

Results are given in Table II and show that indomethacin, paracetamol, clopidogrel, salbutamol, sodic alendronate, diphyllyne, cetirizine, enalapril, nicotinamide, ampicilline, aciclovir, tacrine, omeprazol do not significantly inhibit apoptosis; these drugs can therefore be used for preparing the products of the invention.

On the contrary ambroxol, mesalamine and simvastatine inhibit apoptosis. Therefore on the basis of the results of test 2 these compounds could not be used for preparing the products of the invention.

EXAMPLE F3

Test 3 - experimental in vivo model with N^w-nitro-L-arginine-methyl ester (L-NAME): gastric tolerability (gastrointestinal damage incidence), hepatic (GPT dosage, glutamic-pyruvic transaminase) and cardiovascular (blood pressure) tolerability of some drugs screened as precursors of the compounds of the invention.

The experimental model adopted is according to J. Clin.

Investigation 90, 278-281,1992.

The endothelial dysfunction is evaluated by determining the damage induced by L-NAME administration to the gastrointestinal mucosa, the hepatic damage (GPT increase), and the vascular endothelium or cardiovascular damage as blood hypertension.

The animals (rats, average weight 200 g) are divided in groups as herein below described. The group receiving L-NAME is treated for 4 weeks with said compound dissolved at the concentration of 400 mg/litre in drinking water. The following groups (No. 10 animals for group) are constituted:

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, physiologic solution when by parenteral route),

2° group: treatment: carrier + L-NAME,

B) Groups treated with the drug:

3° group: treatment: carrier + drug,

4° group: treatment: carrier + drug + L-NAME.

The drugs used in the test are paracetamol, doxorubicine, simvastatine, omeprazol and misoprostol. Each drug is administered once a day for 4 weeks.

The maximum tolerated dose of the drug being administered to the animals is determined by evaluating, in a separate dose

scaling up experiment on untreated animals, the appearance in the animals of symptoms such as enteropathy, diarrhoea, depression, tremor, sedation.

At the end of the four weeks access to water is prevented and after 24 hours the animals are sacrificed.

One hour before the sacrifice blood pressure is determined and a blood pressure increase is taken as an indication of a damage being occurred to vascular endothelium.

The damage to the gastric mucosa is evaluated as previously mentioned in test 1 (ex. F1). The hepatic damage is determined by evaluation after the sacrifice of the glutamic-pyruvic transaminase (GPT increase).

The drug meets test 3 and it can therefore be used for preparing the compounds of the invention, when in the group of rats treated with L-NAME + drug + carrier, an higher hepatic damage (higher GPT values) and/or higher gastric damage and/or higher cardiovascular damage (higher blood pressure) are found in comparison with the group treated with the carrier only, or the group treated with carrier + drug, or the group treated with carrier + L-NAME.

The test results are reported in Table IV. The % gastric lesions have been determined as in Test 1. The % GPT and % blood pressure values are referred to the corresponding value found in the animals of the 1st group of the control groups. The average value of the blood pressure in this group was of

105 \pm 8 mmHg.

The results obtained show that paracetamol, doxorubicin and simvastatine cause hepatic damage and gastroenteropathy (GPT values and the gastric lesions are % higher compared both with the corresponding groups treated with the drug, in the absence of L-NAME, and with the controls treated with L-NAME).

These drugs can therefore be used for preparing the products of the invention.

Omeprazol and misoprostol should not instead be used, on the basis of this test, for preparing the products of the invention.

EXAMPLE F4

Test 4: inhibition of the radical production from DPPH of some substances to be used as precursors of B or B1 (ref. Formulas I and II of the invention)

The method is based on a colorimetric test in which DPPH (2,2-diphenyl-1-picryl-hydrazyl) is used as the compound-forming radicals (M.S. Nenseter et Al., Atheroscler. Thromb. 15, 1338-1344, 1995).

Solutions in methanol of the tested substances at a final concentration 100 μ M are initially prepared. 0.1 ml of each of these solutions are added to aliquots of 1 ml of a methanol solution 0.1 M of DPPH and then the final volume is brought to 1.5 ml. After having stored the solutions at room temperature away from light for 30 minutes, the absorbance at the wave

length of 517 nm is read. It is determined the absorbance decrease with respect to the absorbance of a solution containing the same concentration of DPPH.

The efficacy of the test compound to inhibit the production of radicals, or antiradical activity, is expressed by the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are, respectively, the absorbance values of the solution containing the test compound together + DPPH and of the solution containing only DPPH.

The compound meets test 4 if radical production inhibition, as above defined, is equal to or higher than 50%.

In Table V the results obtained with the following substances are reported: N-acetylcysteine, cysteine, ferulic acid, (L)-carnosine, gentisic acid.

Table V shows that N-acetylcysteine, cysteine, ferulic acid, (L)-carnosine, gentisic acid meet test 4 since they inhibit the production of radicals formed from DPPH by more than 50%.

EXAMPLE F5

Antiinflammatory activity and gastric tolerability of the compounds according to the invention in comparison with the corresponding precursor drugs in conditions of endothelial dysfunction induced by L-NAME (N^W -nitro-L-arginine-methyl ester)

The experimental model of Edwards et Al., J. Pathol. 134, 147-156, 1981 was followed.

Groups formed by 10 rats, having an average weigh of 200 g, have been constituted. The groups have been treated with L-NAME dissolved in drinking water (400 mg/l) for two weeks, except one group which constituted the control group.

The drugs were administered by os, at the dose of 10 mg/Kg, in carrier carboxymethylcellulose 1% in water, 5 ml/Kg.

Thus the groups, except the below described control groups, were treated with the drug + L-NAME + carrier.

The following control groups were formed:

1° control group: treatment: carrier.

2° control group: treatment: carrier + L-NAME.

The drugs used in the experiment are the following: diclofenac and the corresponding thioester with (4-nitroxy)butyryl penicillamine (Ex. 26), piroxicam and the corresponding ester with the p-(4-nitroxy)butyryloxy-ferulic acid (Ex. 25), the acetylsalicylic acid and the corresponding thioester with N-acetyl-(4-nitroxy)butyrylcysteine (Ex. 24).

After two weeks from the beginning of the experiment the animals were subjected to three consecutive injections of air by subcutaneous route, in the dorsal part of the animal, according to the following procedure:

- first injection: 20 ml,
- after three days from the first injection: 10 ml.

- after 6 days from the first injection: the same amount of 10 ml.

The animals were then fasted until the following morning. One hour before the percutaneous injection with carragenine (2 ml of a 1% carragenine solution in water) in the inflammatory exudate, the treated animals received by os the carrier or one of the tested compounds dissolved or suspended in the carrier. The animals were sacrificed after 6 hours from the injection of the carragenine solution. The inflammatory exudate was collected and measured to evaluate the leucocyte infiltration.

In Table VI the antiinflammatory activity is expressed as % inhibition of the leucocyte infiltration with respect to the leucocyte infiltration value found in the animals treated with the carrier and pretreated with L-NAME, the % inhibition of the gastrointestinal damage was evaluated as previously described in Test 1 (ex. 1), and the % blood pressure was evaluated one hour before the sacrifice and referred to that of the 1st control group (treatment: carrier). In this group of animals the average pressure value was of 108 ± 10 mmHg.

Table VI shows that the compounds of the invention are as active as the corresponding precursors in the antiinflammatory activity test, but in the confront of the latter they reduce the damage to the cardiovascular endothelium (lower % increase of blood pressure with respect to that of the corresponding precursor), and besides reduce, or do not give at all, gastric

damage.

EXAMPLE F6

In a second apoptosis experiment indomethacin and the indomethacin thioester with N-acetyl-(4-nitroxy)butyryl cysteine (Ex. 3) according to the present invention were compared. The results are reported in Table III, and show that the compound of the invention inhibits, differently from the precursor, the apoptosis induced by cumene hydroperoxide (CIP).

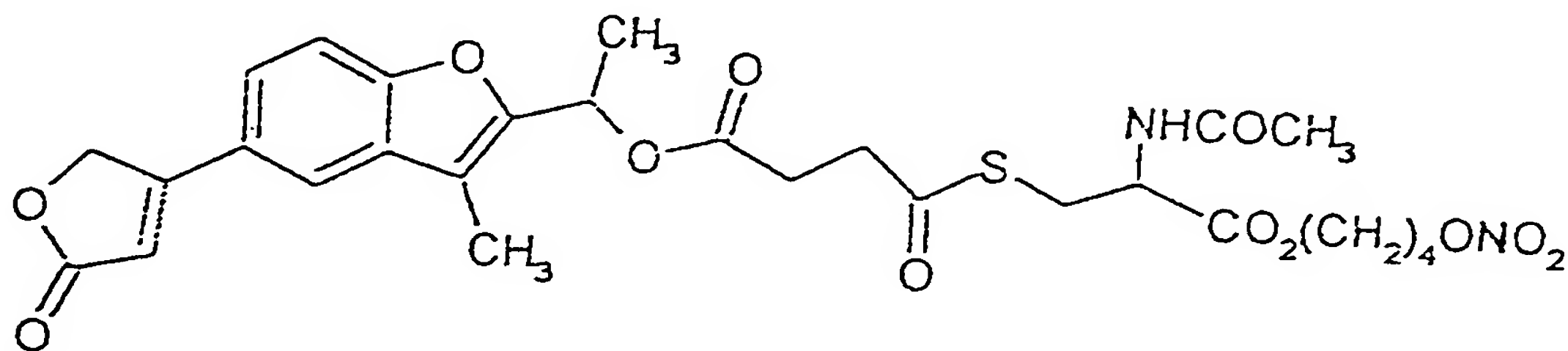
EXAMPLE F7

Gastric tolerability of some drugs used as precursors and of the corresponding compounds according to the invention.

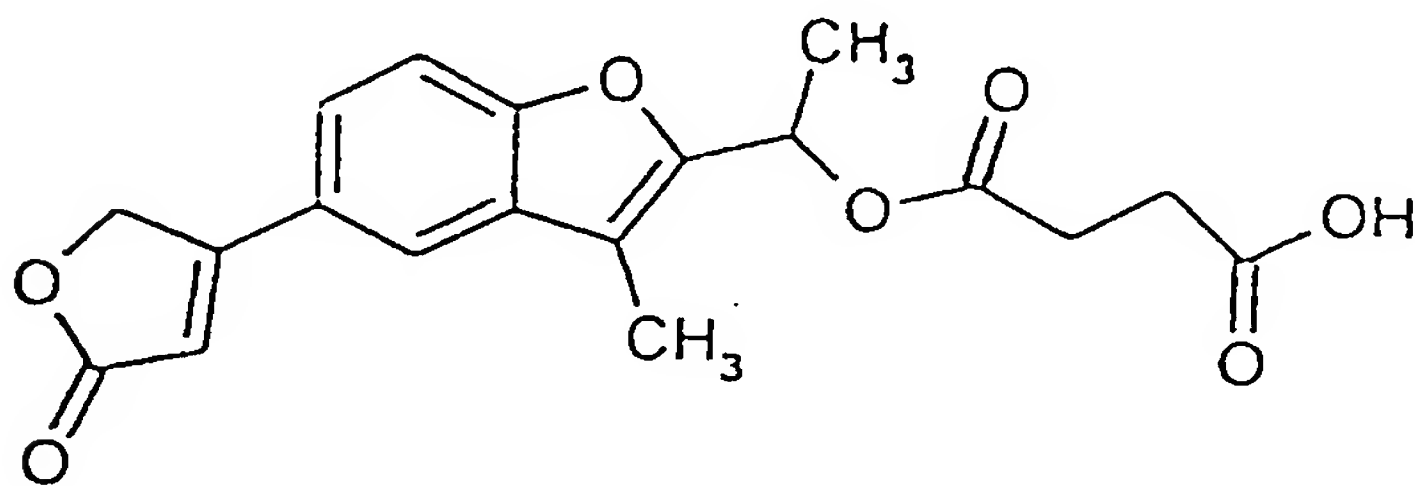
The test for gastrointestinal damage of Example F5 was repeated but omitting the pretreatment of animals with L-NAME. The tested drugs, thereof administered doses and results are reported in Table VII. From the Table it is drawn that gastropathy incidence is much lower in the groups treated with the compounds of the invention in the confront of the groups treated with the corresponding precursors.

EXAMPLE 27

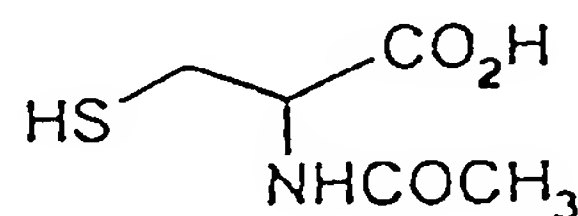
Synthesis of (S)-N-acetyl-S-[[1-[5-(2,5-dihydro-5-oxo-3-furanyl)-3-methyl-2-benzofuranyl]ethyloxy]-4-oxo-butanoyl]cysteine (4-nitroxy)butyl ester of formula



wherein the precursor is benfurodil hemisuccinate of formula (XXXI) and the precursor of B is N-acetylcysteine (formula CVIII)



(XXXI)



(CVIII)

The compound is synthesized according to the process described in Example 4. Yield 25%.

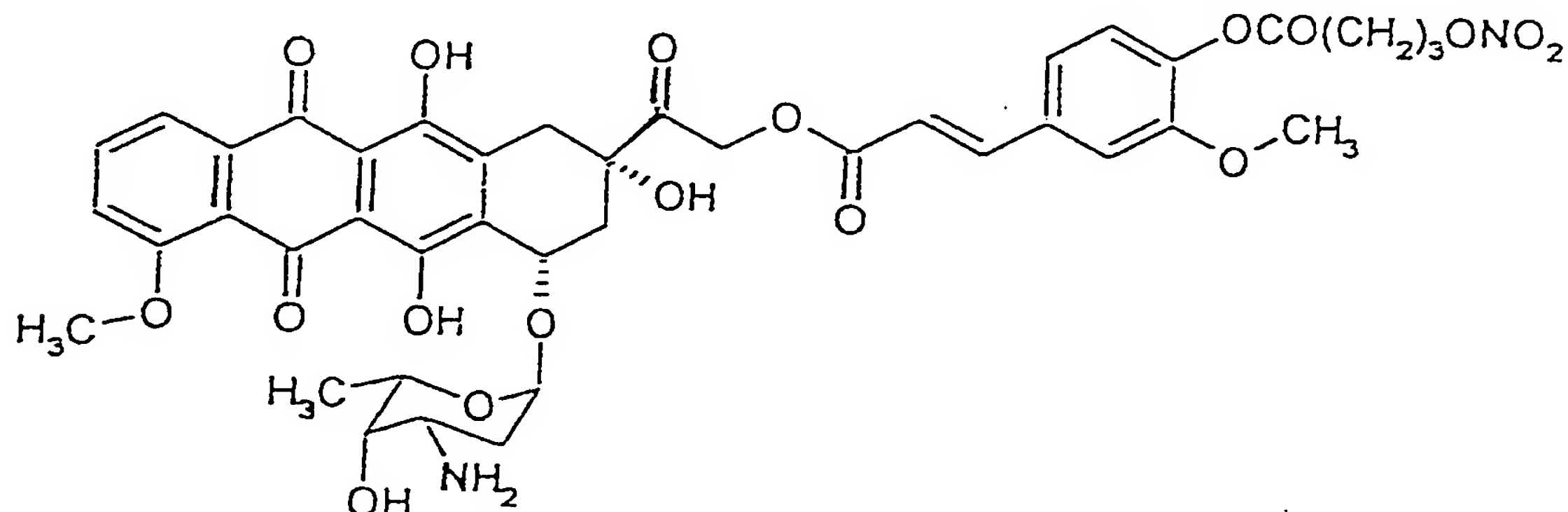
Elementary analysis

Calculated C: 54.19% H: 5.20% N: 4.51% S: 5.17%

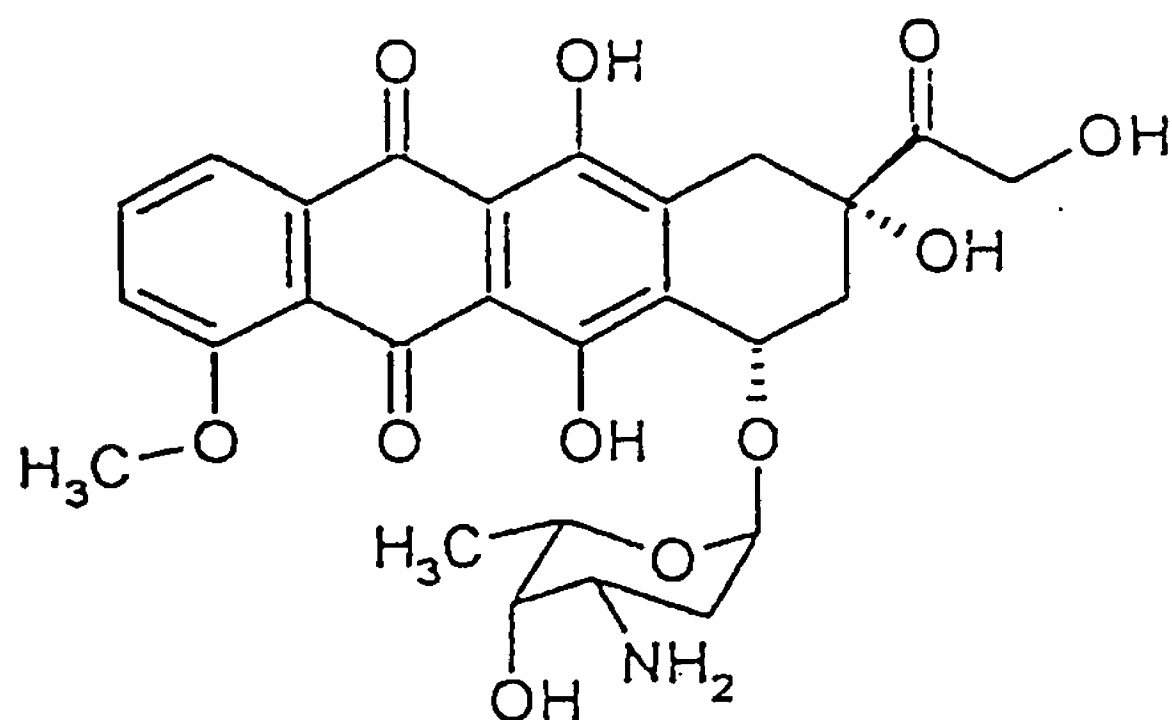
Found C: 54.25% H: 5.22% N: 4.47% S: 5.15%

EXAMPLE 28

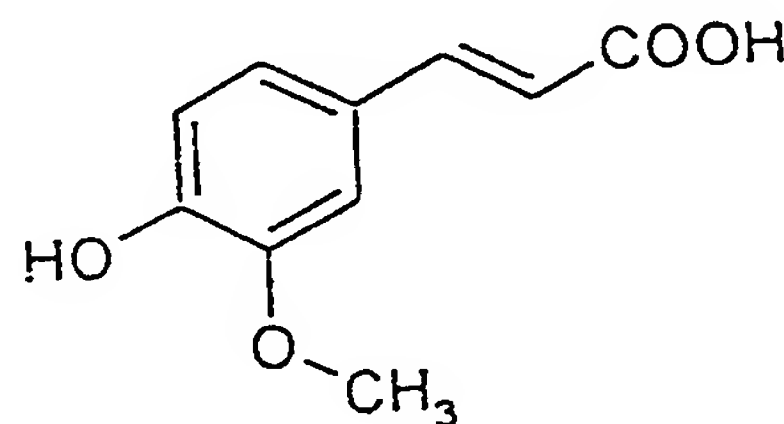
Synthesis of (8S-cis)-10[(3-amino,2,3,6-tri-deoxy- α -L-lyxo-exo pyranosyl)oxy]-7,8,9,10-tetrahydro,6,8,11-trihydroxy-8-[[[3-methoxy-4-(4-nitroxybutanoyl)phenyl]-2-trans-propenoyl-oxy] methyl-oxo]-1-methoxy-5,12-naphtacenedione of formula



wherein the precursor is doxorubicin of formula (XXXII) and the precursor of B is ferulic acid of (formula DII)



(XXXII)



(DII)

The compound is synthesized according to the process described in Example 9. Yield 11%.

Elementary analysis

Calculated	C: 57.88%	H: 4.98%	N: 3.29%
Found	C: 57.91%	H: 5.02%	N: 3.27%

EXAMPLE F8

Example F1 was repeated with four groups of rats (each group of ten animals), all of them receiving NEM, and orally administered as it follows :

- a. control group : the vehicle formed of an aqueous suspension 1% w/v of carboxymethylcellulose,
- b. one group (group b - comparative) administered at the same time with 5 mg/Kg (0.014 mmoles/Kg) of indomethacin + 2.3 mg/Kg (0.014 mmoles/Kg) of N-acetylcysteine in the same above vehicle,
- c. one group (group c - comparative) administered at the same time with 6.6 mg/Kg (0.014 mmoles/Kg) of indomethacin 4-(nitroxy)butyl ester, synthetized according to the method disclosed in WO 95/09831, + 2.3 mg/Kg (0.014 mmoles/Kg) of N-acetylcysteine in the same above vehicle,
- d. one group (group d) administered with 8,7 mg/Kg (0.014 mmoles/Kg) of the indomethacin thioester with N-acetyl-(4-nitroxy)butyryl cysteine (ref. Ex. 3), in the above same vehicle.

The results are reported in Table VIII and show that the mixtures administered respectively to groups b and c (comparatives), differently from the compound of the invention administered to group d, were almost ineffective (group b) or much less effective (group c) in reducing gastric lesions.

Table I

Test 1 : Gastric tolerability of drugs representative of the drug classes illustrated in the present invention in animals not treated or treated with NEM (oxidative stress conditions). The % incidence is calculated from the ratio between the number of animals found with gastric lesions and that total of the group.			
Compound	dose (mg/Kg) /admin. route	Gastro-enteropathy (% incidence)	
		without NEM	with NEM
carrier		0	0
Indomethacin	7.5/p.o.	0	100
Ambroxol	25/p.o.	0	80
Mesalamine	750/i.c.	0	60
Alendronate	15/p.o.	0	90
Tacrine	1/s.c.	0	100
Omeprazol	30/s.c.	0	0
Misoprostol	0.5/s.c.	0	0

p.o. = per os; i.c. = by intracolonic route;
s.c. = by subcutaneous route.

Table II

Test 2 : Inhibition of apoptosis (DNA fragmentation) induced by CIP in the endothelial cells in the presence of compounds representative of the drug classes illustrated in the present invention.	
Compound	Apoptosis % with respect to the controls treated only with CIP
Indomethacin	95
Paracetamol	120
Clopidogrel	110
Salbutamol	90
Ambroxol	70
Alendronate	160
Diphylline	95
Cetirizine	115
Enalapril	80
Nicotinamide	98
Ampicilline	94
Aciclovir	95
Mesalamine	74
Tacrine	90
Simvastatine	72
Omeprazol	90

Table III

Test 2 : comparison of the inhibition of apoptosis (DNA fragmentation), induced by CIP in endothelial cells in the presence of indomethacin and of a corresponding ester according to the present invention.	
Compound	Apoptosis % with respect to the controls treated only with CIP
Indomethacin (comp.)	95
Indomethacin thioester with N-acetyl-(4-nitroxy)butyryl cysteine (ref. Ex. 3)	20

Table IV

Test 3 : Gastric tolerability (gastrointestinal damage incidence), hepatic (GPT dosage, glutamic-pyruvic transaminase), and cardiovascular (blood pressure) of some compounds representative of the drug classes illustrated in the present invention in conditions of endothelial trouble induced by L-NAME. The results relating to the blood pressure and GPT are expressed as % values with respect to those found in the animals treated with the only carrier, without L-NAME.							
Compound	dose mg/Kg /administ. route	Blood pressure %		GPT %		Gastroenteropathy %	
		without L-NAME	with L-NAME	without L-NAME	with L-NAME	without L-NAME	with L-NAME
Carrier		100	152	100	155	0	30
Paracetamol	300/i.p.	108	155	180	500	20	90
Doxorubicine	1/i.p.	120	145	195	360	30	100
Simvastatin	50/p.o.	85	148	122	220	0	60
Omeprazol	30/s.c.	100	150	100	160	0	10
Misoprostol	0.5/s.c.	100	142	100	160	0	5

Table V

Test 4: Screening of the effectiveness of the listed compounds in inhibiting radical production from DPPH.	
Compound	% inhibition radicals from DPPH
Solvent	0
N-acetylcysteine	100
Cysteine	100
Ferulic acid	100
(L)-carnosine	80
Gentisic acid	80
Penicillamine	100

Table VI

Antiinflammatory activity (leucocyte infiltration with respect to the animals treated with carrier and pretreated with L-NAME), gastric tolerability and blood pressure (with respect to the animals not pretreated with L-NAME) of some drugs and of the corresponding compounds according to the present invention					
Compound	dose mg/kg	Leucocyte infiltration % inhibition	Blood pressure %	Gastropathy % incidence	
Carrier	-	-	145	30	
Diclofenac (comp.)	10	68	155	100	
Diclofenac thioester with (4-nitroxy)butyryl penicillamine (Ex. 26)	10	70	115	20	
Piroxicam (comp.)	10	78	145	100	
Piroxicam ester with p-(4- nitroxy)butyryloxy ferulic acid (Ex. 25)	10	75	110	10	
Acetylsalicylic acid (comp.)	50	60	160	100	
Thioester acetylsali- cyclic acid with N-acetyl-(4- nitroxy) butyryl cysteine (Ex. 24)	50	55	110	0	

Table VII

Test on gastric tolerability of the listed drugs and of the corresponding derivatives according to the present invention performed on rats not pretreated with L-NAME		
Compound	dose mg/Kg	Gastropathy & incidence
Carrier	-	-
Diclofenac	20/p.o.	70
Diclofenac derivative Ex. 26	20/p.o.	0
Ambroxol	100/p.o.	60
Ambroxol Derivative Ex. 9	100/p.o.	10
Alendronate	100/p.o.	90
Alendronic acid Derivative Ex. 10	100/p.o.	20
Tacrine	10/s.c.	80
Tacrine Derivative Ex. 17	10/s.c.	20

Table VIII

Test on gastric tolerability following oral administration of NEM (Ex. F8)		
groups	dose mg/Kg p.o.	Gastropathy % incidence
controls	-	-
group b - comparative mixture indomethacin (A) + N-acetylcysteine (B)	5 (A) + 2.3 (B)	90
group c - comparative mixture indomethacin 4-(nitroxy)butyl ester (C) + N-acetylcysteine (B)	6.6 (C) + 2.3 (B)	40
group d indomethacin thioester with N-acetyl-(4-nitroxy)butyryl cysteine	8.7	10

CLAIMS

1. Compounds or their salts having the following general formulas (I) and (II):



wherein:

s = is an integer equal to 1 or 2, preferably s = 2;

A = R—T₁—, wherein

R is the drug radical and

T₁ = (CO)_t or (X)_{t'}, wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = —T_B—X₂—T_{BI}— wherein

T_B and T_{BI} are equal or different;

T_B = (CO) when t = 0, T_B = X when t' = 0, X being as above defined;

T_{BI} = (CO)_{tx} or (X)_{txx} wherein tx and txx have the 0 or 1 value; with the proviso that tx = 1 when txx = 0, and tx = 0 when txx = 1; X is as above defined;

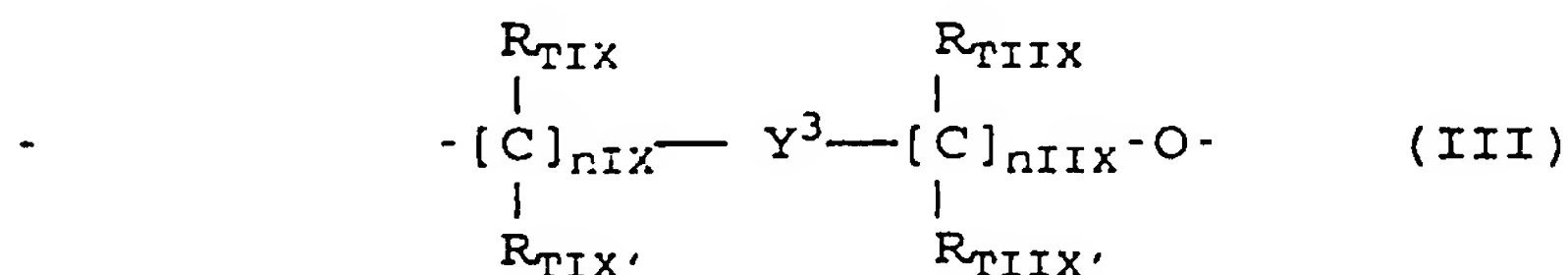
X₂ is a bivalent bridging bond as defined below;

C is the bivalent —T_C—Y— radical, wherein

T_C = (CO) when tx = 0, T_C = X when txx = 0, X being as above defined;

Y is an alkyleneoxy group R'O wherein R' is linear or

branched when possible C_1-C_{20} , preferably having from 1 to 6 carbon atoms, most preferably 2-4, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring may have side chains of R' type, R' being as above defined; or



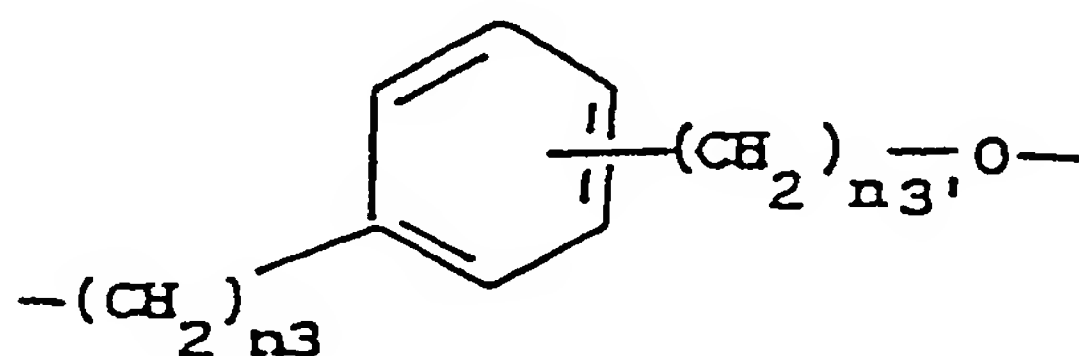
wherein:

n_{IX} is an integer between 0 and 3, preferably 1;

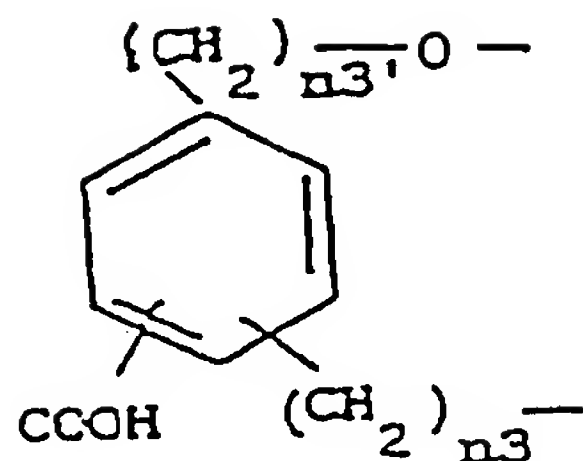
n_{IIX} is an integer between 1 and 3, preferably 1;

R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$, equal to or different from each other are H or a linear or branched C_1-C_4 alkyl; preferably R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$ are H.

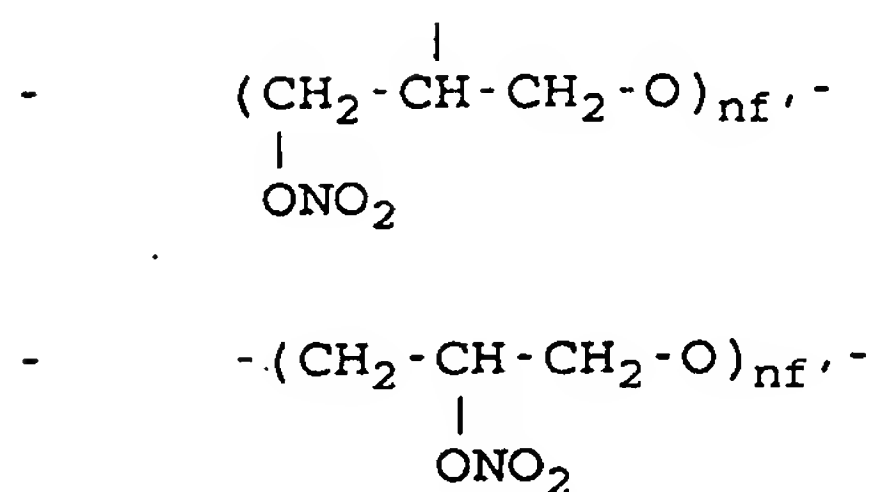
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen atom, said ring having 5 or 6 atoms.



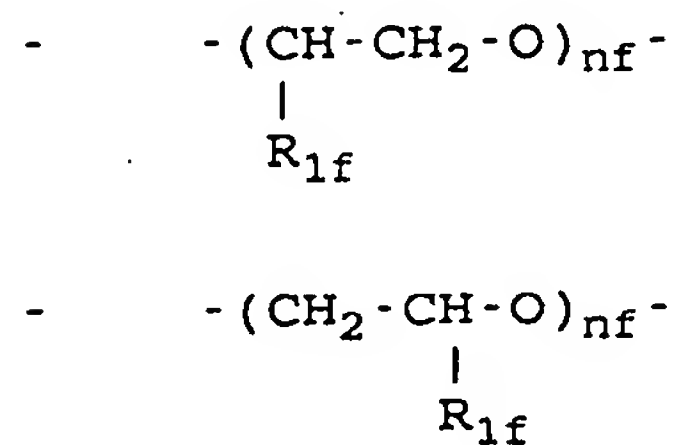
wherein n_3 is an integer from 0 to 3 and $n_{3'}$ is an integer from 1 to 3;



wherein n_3 and n_3' have the above mentioned meaning



wherein n_f' is an integer from 1 to 6 preferably from 1 to 4;

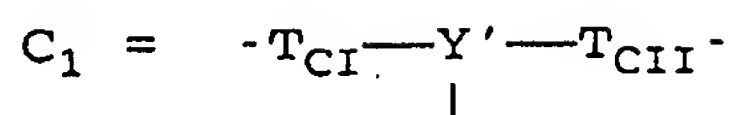


wherein $\text{R}_{1f} = \text{H}, \text{CH}_3$ and n_f is an integer from 1 to 6; preferably from 1 to 4;

preferably $\text{Y} = -\text{R}'\text{O}-$ wherein R' is as above defined;
preferably R' is a $\text{C}_1\text{-C}_6$ alkyl;



wherein:



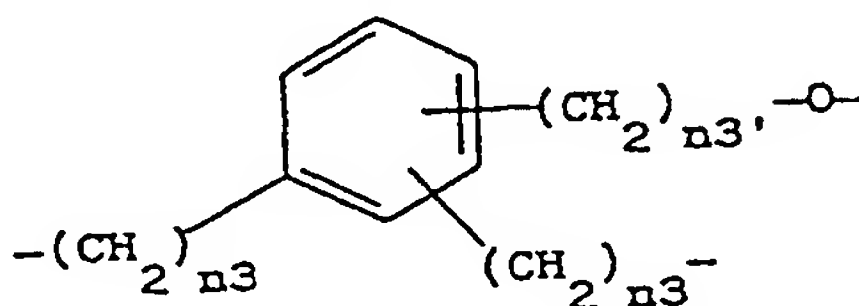
wherein T_{CI} and T_{CII} are equal or different,

$T_{CI} = (CO)$ when $t = 0$, $T_{CI} = X$ when $t' = 0$, X being as above defined;

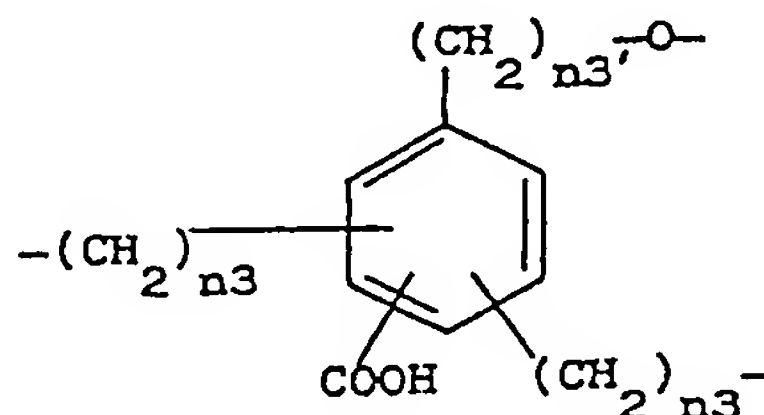
$T_{CII} = (CO)_{tI}$ or $(X)_{tII}$, wherein tI and tII have the 0 or 1 value; with the proviso that $tI = 1$ when $tII = 0$, and $tI = 0$ when $tII = 1$; X is as above defined;

Y' is as Y above defined, but with three free valences instead of two, preferably:

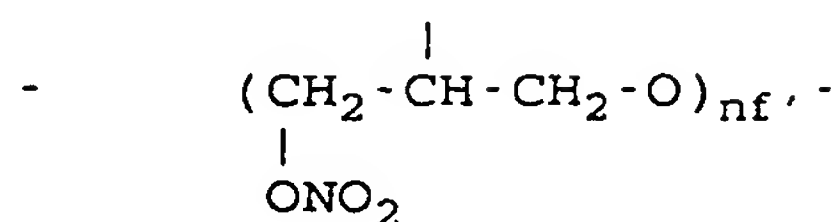
- a $-R'O-$ group wherein R' is as above defined,
 $|$
 preferably an alkyl from 1 to 6 carbon atoms, most preferably 2-4, or



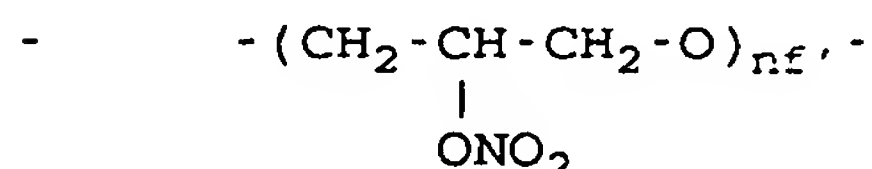
wherein $n3$ is an integer from 0 to 3 and $n3'$ is an integer from 1 to 3;



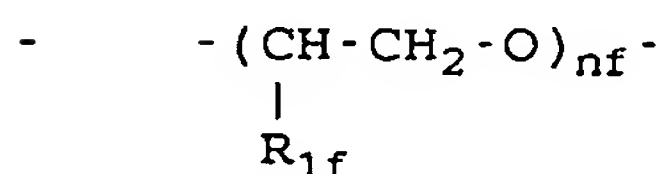
wherein n_3 and n_3' have the above mentioned meaning;



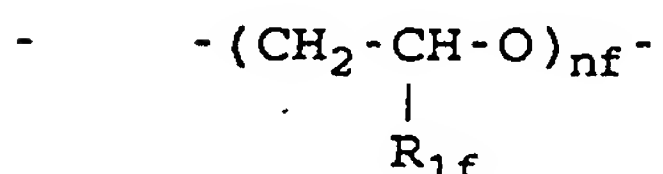
wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein n_f' is an integer from 1 to 6 preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein $\text{R}_{1f} = \text{H}, \text{CH}_3$ and n_f is an integer from 1 to 6; preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;

preferably $\text{Y}' = - \text{R}'\text{O}-$ wherein R' is a linear or

branched $\text{C}_2 - \text{C}_4$, the oxygen which in Y' is covalently linked to the $-\text{N}(\text{O})_s$ group is at the end of the free bond indicated in the formula of C_1 ;



wherein X_{2a} is a monovalent radical as defined below,

$T_{BII} = (CO)$ when $tI = 0$, $T_{BII} = X$ when $tII = 0$, X being as above defined;

- X_2 , bivalent radical is such that the corresponding precursor of B: $-T_B-X_2-T_{BI}-$ meets test 4, precursor in which the T_B and T_{BI} free valence are each saturated with $-OZ$, $-Z$, or with $-Z^I-N-Z^{II}$, Z^I and Z^{II} being equal or different and have the Z values as defined below, depending on that T_B and/or $T_{BI} = CO$ or X , in connection with the values of t , t' , tx and txx ;
- X_{2a} monovalent radical, such that the corresponding precursor of B_1 $-T_{BII}-X_{2a}$ meets test 4, precursor wherein the T_{BII} free valence is saturated with $-OZ$, $-Z$ or with $-Z^I-N-Z^{II}$, Z^I and Z^{II} being equal or different and having the Z values as defined below, depending on that $T_{BII} = CO$ or X , in connection with the tI and tII values;
- the drug $A = R-T_1-$, wherein the free valence is saturated as indicated hereinafter:
- when $t' = 0$ with:
 - $O-Z$ wherein $Z = H$ or R_{1a} , R_{1a} being a linear or branched when possible C_1-C_{10}

alkyl, preferably C_1-C_5 , or with
 $-Z^I-N-Z^{II}$, Z^I and Z^{II} being as above
 defined,

- when $t = 0$ with $-Z$, wherein Z is as above
 defined,

with the proviso that the drug is not a steroid, is such
 to meet at least one of tests 1-3;

- wherein test 1 (NEM) is a test in vivo carried out on
 four groups of rats (each formed by 10 rats), the controls
 (two groups) and the treated (two groups) of which one
 group of the controls and one group of the treated
 respectively are administered with one dose of 25 mg/kg
 s.c. of N-ethylmaleimide (NEM), the controls being treated
 with the carrier and the treated groups with the carrier
 + the drug of formula $A = R-T_1-$ wherein the free valence
 is saturated as above indicated, administering the drug at
 a dose equivalent to the maximum one tolerated by the rats
 that did not receive NEM, i.e. the highest dose
 administrable to the animal at which there is no manifest
 toxicity, i.e. such as to be symptomatologically
 observable; the drug complies with test 1, i.e. the drug
 can be used to prepare the compounds of general formula
 (I) and (II), when the group of rats treated with NEM +
 carrier + drug shows gastrointestinal damages, or in the
 group treated with NEM + carrier + drug are observed ga-
 strointestinal damages greater than those of the group
 treated with the carrier, or of the group treated with the
 carrier + drug, or of the group treated with the carrier

+ NEM;

- wherein test 2 (CIP) is a test in vitro wherein human endothelial cells from the umbilical vein are harvested under standard conditions, then divided into two groups (each group replicated five times), of which one is treated with a mixture of the drug 10^{-4} M concentration in the culture medium, the other group with the carrier; then cumene hydroperoxide (CIP) having a 5 mM concentration in the culture medium is added to each of the two groups; the drug meets test 2, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), if a statistically significant inhibition of the apoptosis (cellular damage) induced by CIP is not obtained with $p < 0.01$ with respect to the group treated with the carrier and CIP;

- wherein test 3 (L-NAME) is a test in vivo carried out on four groups of rats (each group formed by 10 rats) for 4 weeks and receiving drinking water, the controls (two groups) and the treated (two groups), of which one group of the controls and of the treated respectively receives in the above 4 weeks drinking water added of N- ω -nitro-L-arginine methyl ester (L-NAME) at a concentration of 400 mg/litre, the controls in the 4 weeks being administered with the carrier and the treated in the 4 weeks with the carrier + the drug, administering the carrier or the drug + carrier once a day, the drug being administered at the maximum dose tolerated by the group of rats not pretreated with L-NAME, i.e., the highest dose administrable to animals at which no manifest toxicity appears, i.e. such

as to be symptomatologically observable; after the said 4 weeks, the water supply is stopped for 24 hours and then sacrificed, determining the blood pressure 1 hour before sacrifice, and after sacrifice of the rats determining the plasma glutamic pyruvic transaminase (GPT) after sacrifice, and examining the gastric tissue; the drug meets test 3, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when in the group of rats treated with L-NAME + carrier + drug, greater hepatic damages (determined as higher values of GPT) and/or gastric and/or cardiovascular damages (determined as higher values of blood-pressure) are found in comparison respectively with the group treated with the carrier alone, or with the group treated with the carrier + drug, or with the group treated with the carrier + L-NAME;

- the precursors of B or B₁ with the free valences saturated as above defined must meet test 4: it is an analytical determination carried out by adding portions of methanol solutions of the precursor of B or B₁ at a 10⁻⁴ M concentration, to a methanol solution of DPPH (2,2-di-phenyl-1-picryl hydrazyl - free radical); after having maintained the solution at room temperature away from light for 30 minutes, it is read the absorbance at the wave length of 517 nm of the test solution and of a solution containing only DPPH in the same amount as in the test solution; and then the inhibition induced by the precursor towards the radical production by DPPH is calculated as a percentage by means of the following

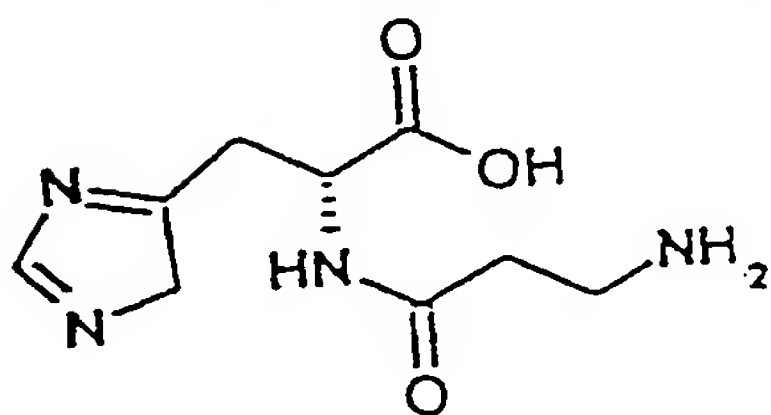
formula:

$$(1 - A_s/A_c) \times 100$$

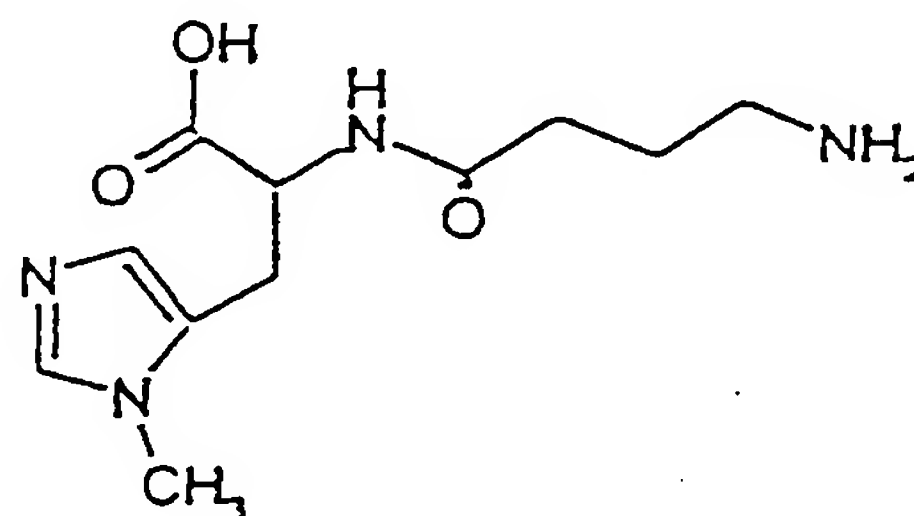
wherein A_s and A_c are respectively the absorbance values of the solution containing the test compound + DPPH and that of the solution containing only DPPH; the precursor complies with test 4 when the percentage of inhibition as above defined is equal to or higher than 50%.

2. Compounds according to claim 1 wherein the precursor compound of B or B₁ is selected from the following classes of compounds:

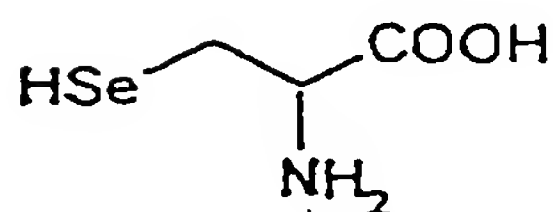
- Aminoacids, selected from the following: L-carnosine (formula CI), anserine (CII), selenocysteine (CIII), selenomethionine (CIV), penicillamine (CV), N-acetyl-penicillamine (CVI), cysteine (CVII), N-acetyl-cysteine (CVIII), glutathione (CIX) or its esters, preferably ethyl or isopropyl ester:



(CI)



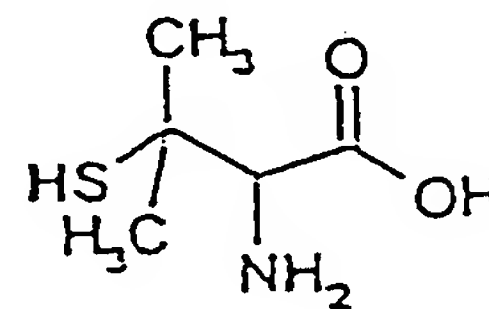
(CII)



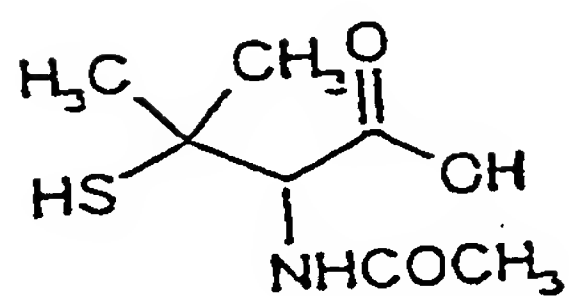
(CIII)



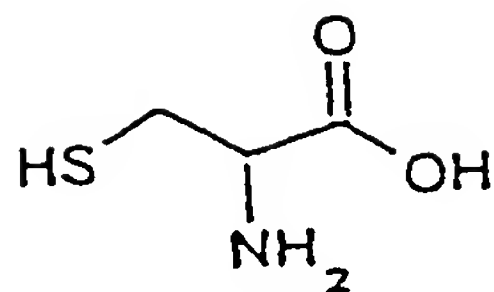
(CIV)



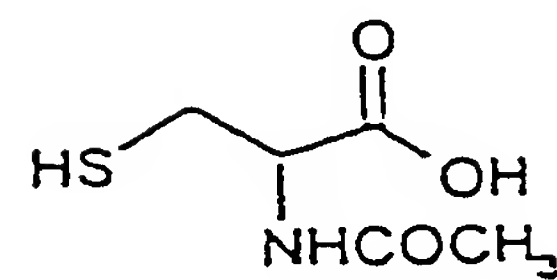
(CV)



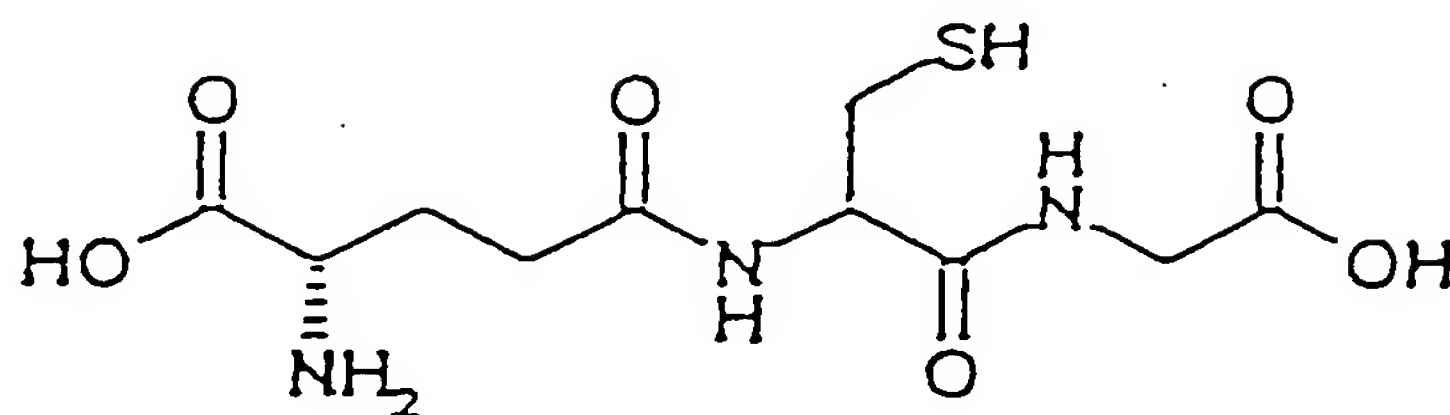
(CVI)



(CVII)

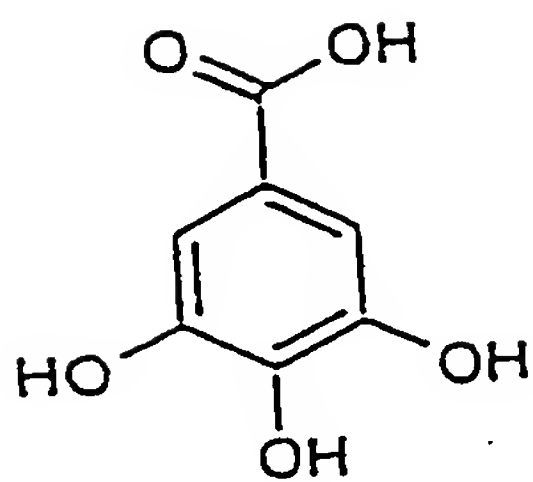


(CVIII)

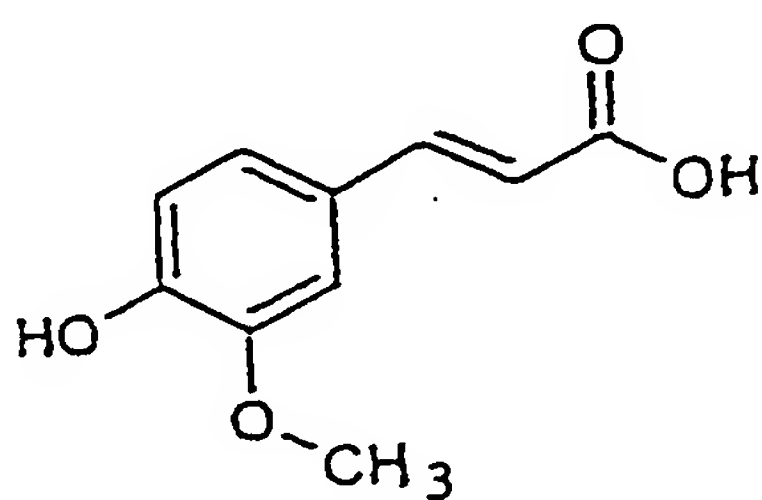


(CIX)

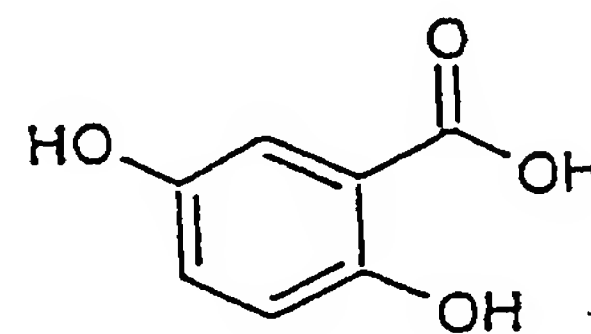
hydroxyacids, selected from the following: gallic acid (formula DI), ferulic acid (DII), gentisic acid (DIII), citric acid (DIV), caffeic acid (DV), hydro caffeic acid (DVI), p-coumaric acid (DVII), vanillic acid (DVIII), chlorogenic acid (DIX), kynurenic acid (DX), syringic acid (DXI):



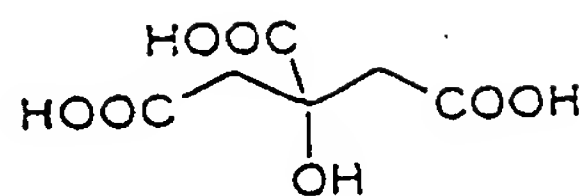
(DI)



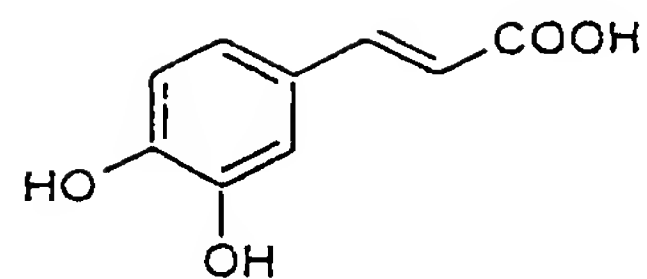
(DII)



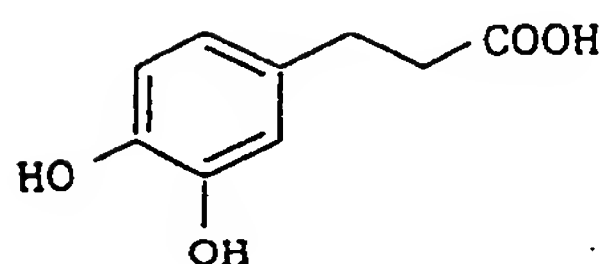
(DIII)



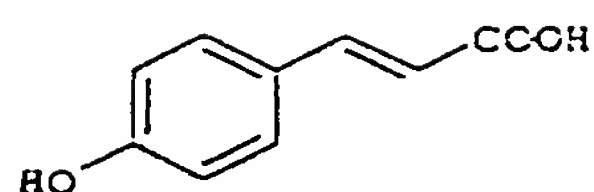
(DIV)



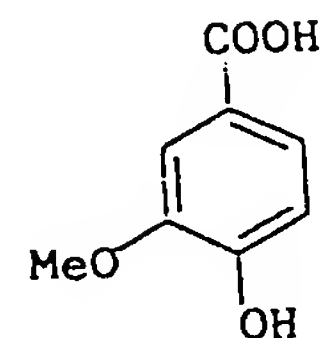
(DV)



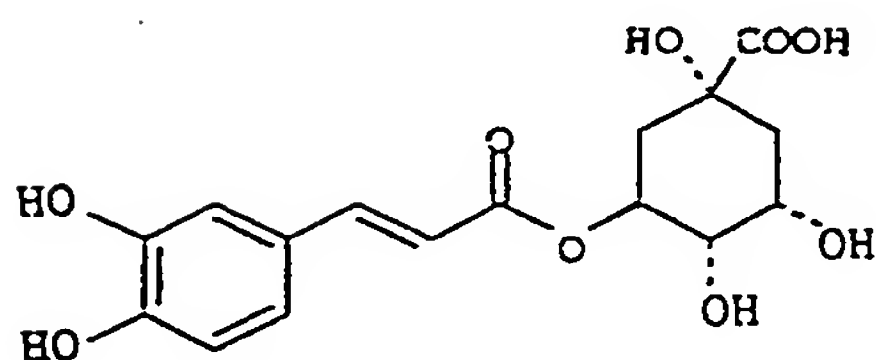
(DVI)



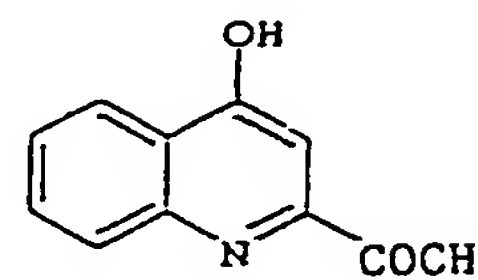
(DVII)



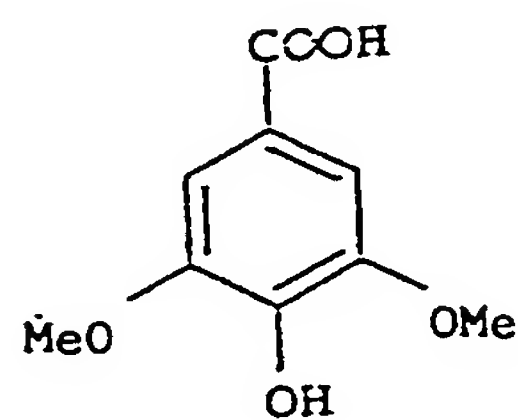
(DVIII)



(DIX)



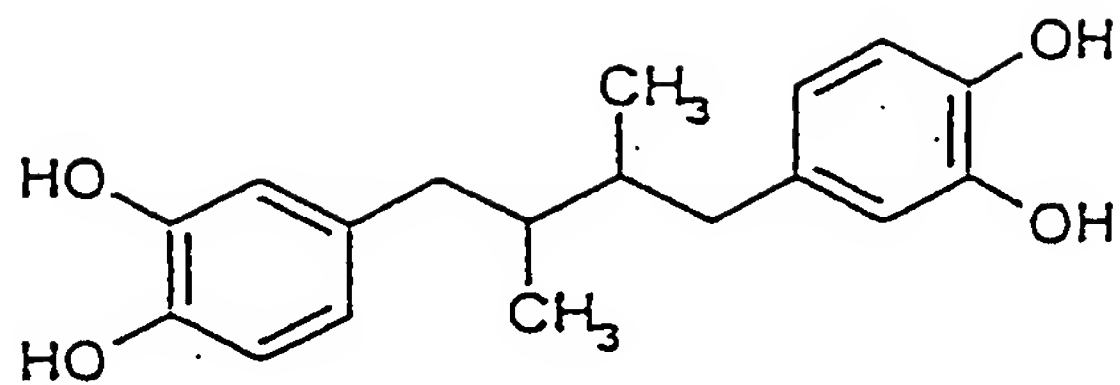
(DX)



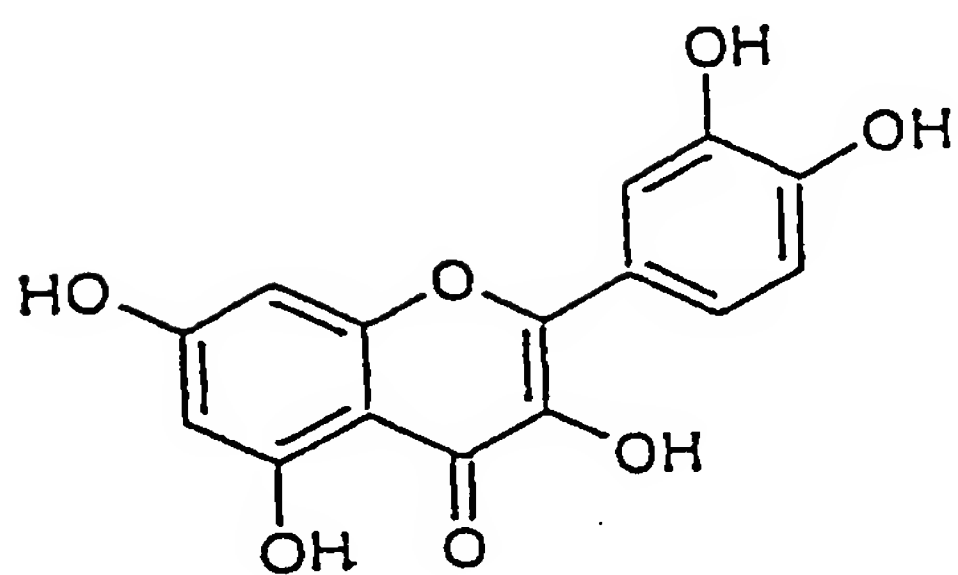
(DXI)

Aromatic and heterocyclic mono- and polyalcohols, selected from the following: nordihydroguaiaretic acid (EI), quercetin (EII), catechin (EIII), kaempferol (EIV), sulphurethyne (EV), ascorbic acid (E-

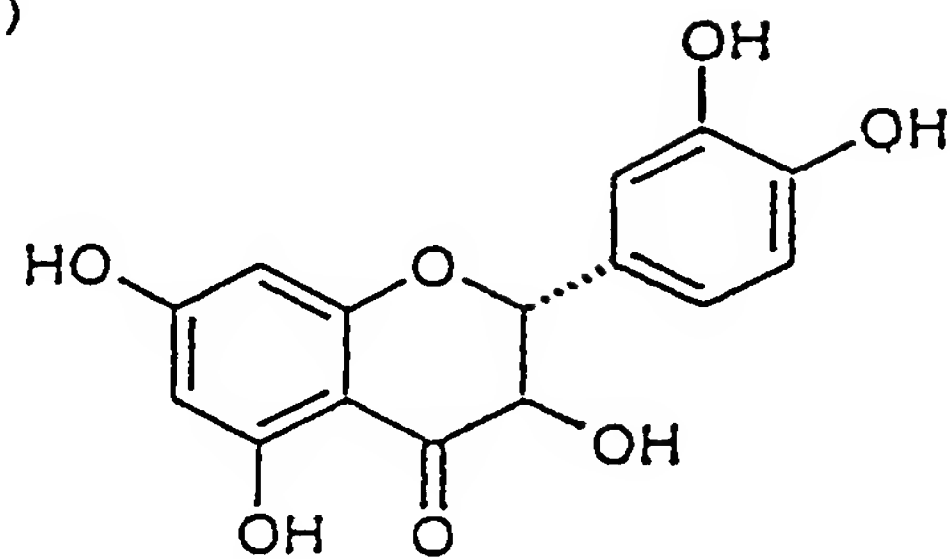
VI), isoascorbic acid (EVII), hydroquinone (EVIII), gossypol (EIX), reductic acid (EX), methoxyhydroquinone (EXI), hydroxyhydroquinone (EXII), propyl gallate (EXIII), saccharose (EXIV), vitamin E (EXV), vitamin A (EXVI), 2-quinolol (EXVII), 3-ter-butyl-4-hydroxyanisole (EXVIII), 3-hydroxyflavone (EXIX), 3,5-ter-butyl-p-hydroxytoluene (EXX), p-ter-butyl phenol (EXXI), timolol (EXXII), xibornol (EXXIII), 3,5-di-ter-butyl-4-hydroxybenzyl-thioglycolate (EXXIV), 4'-hydroxybutyranilide (EXXV), guaiacol (EXXVI), tocol (EXXVII), isoeugenol (EXXVIII), eugenol (EXXIX), piperonyl alcohol (EXXX), allopurinol (EXXXI), conyferyl alcohol (EXXXII), 4-hydroxyphenetyl alcohol (EXXXIII), p-coumaric alcohol (EXXXIV), curcumin (EXXXV):



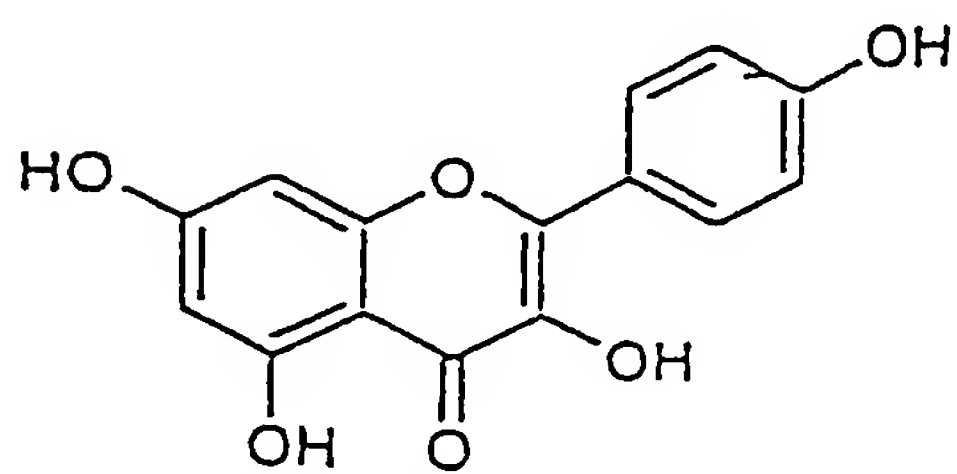
(EI)



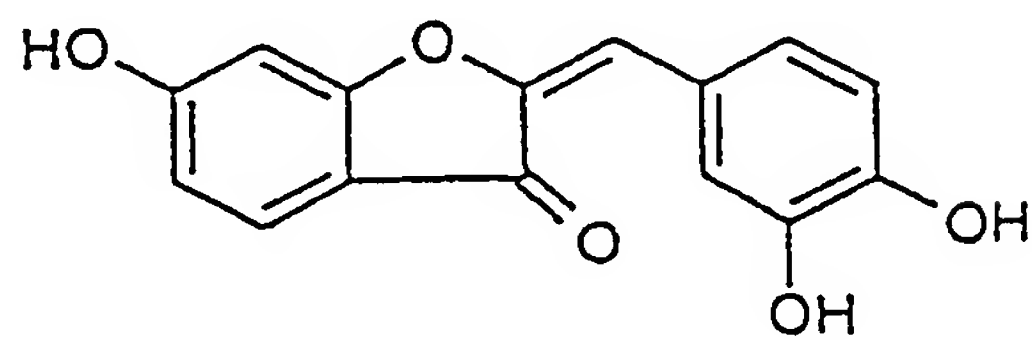
(EII)



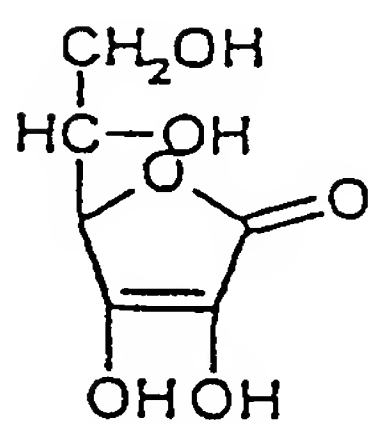
(EIII)



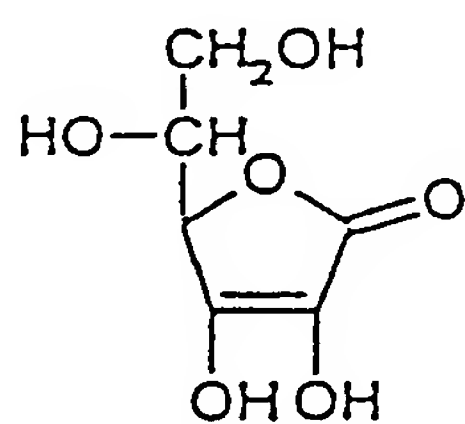
(EIV)



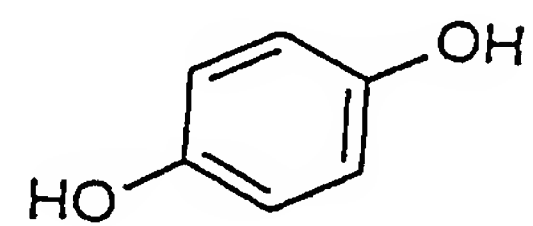
(EV)



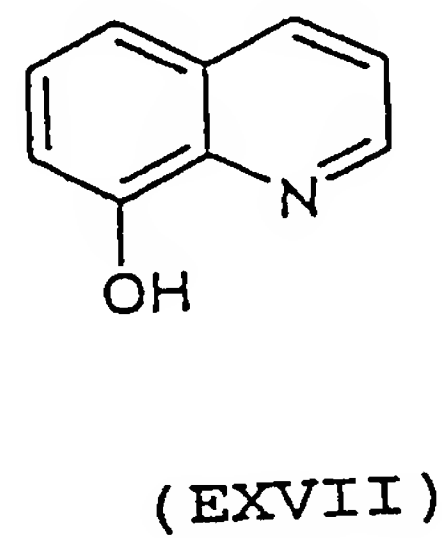
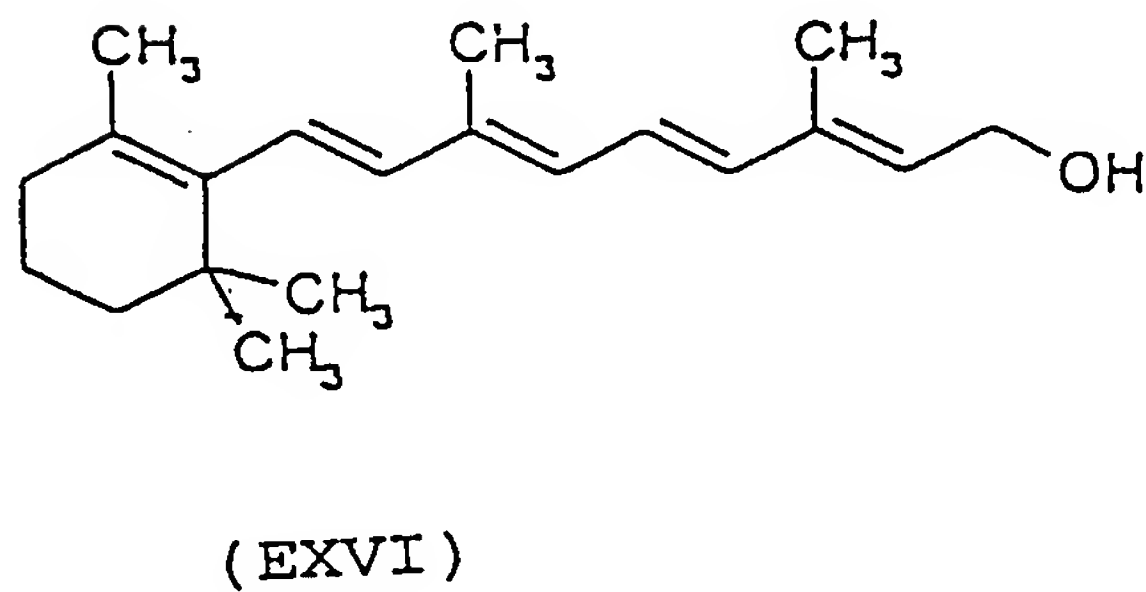
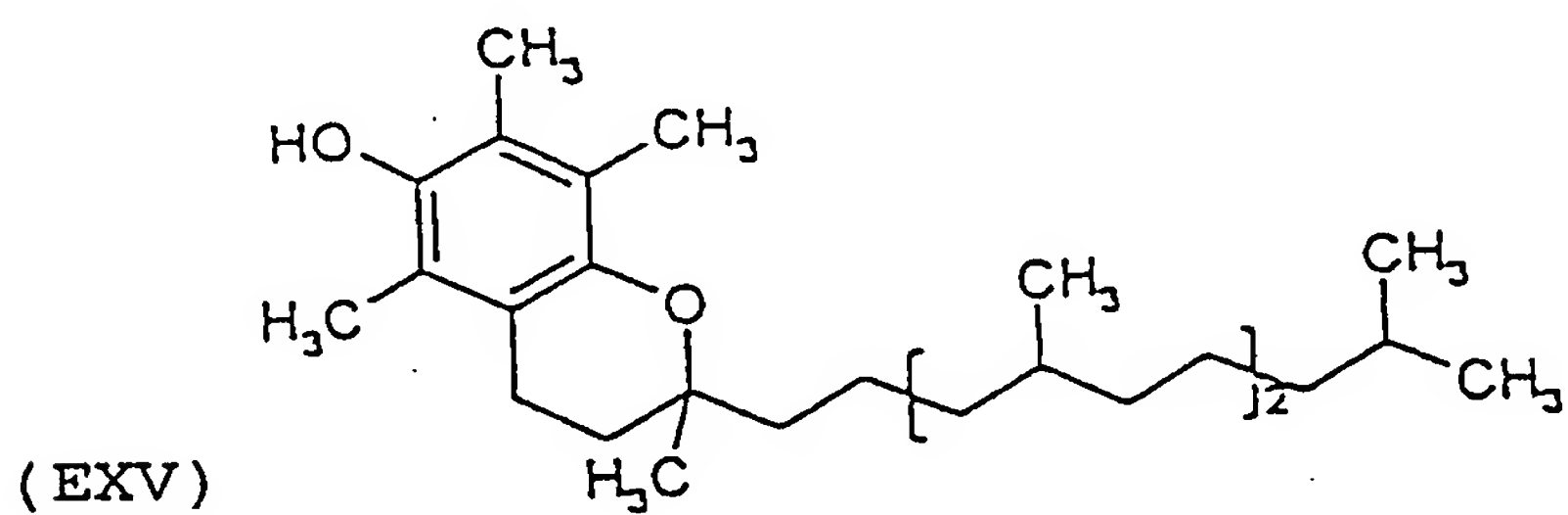
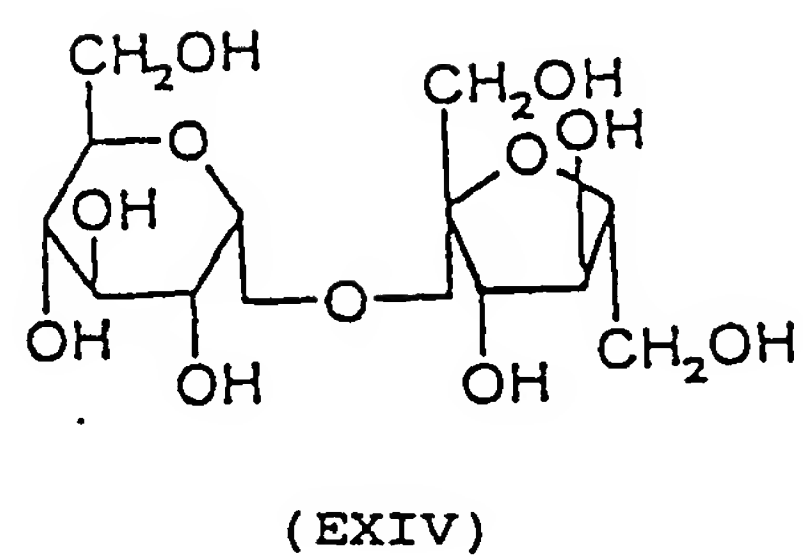
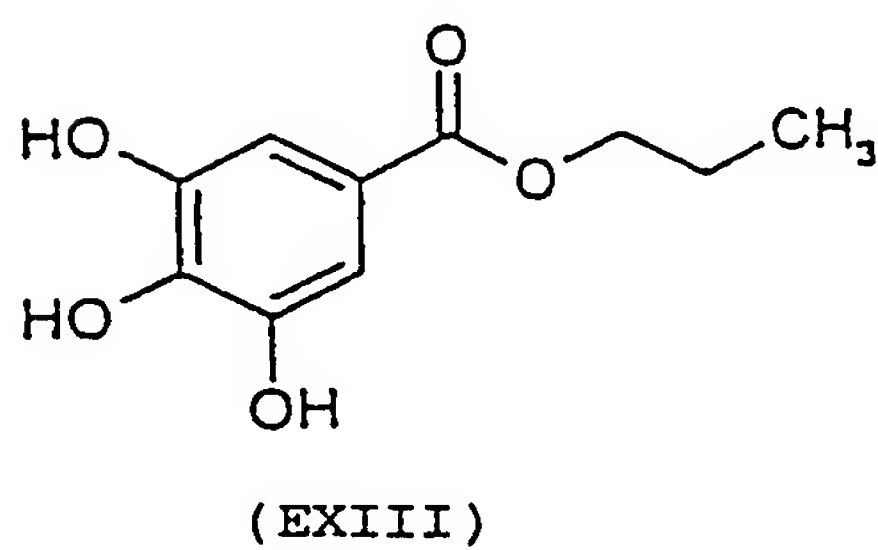
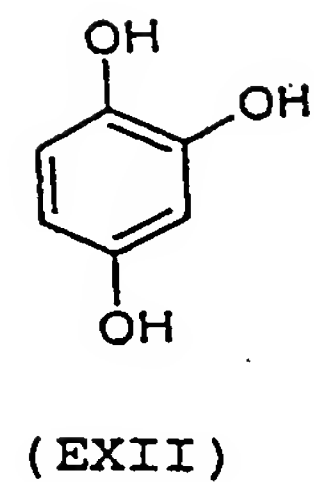
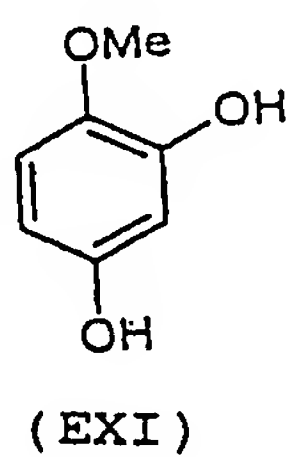
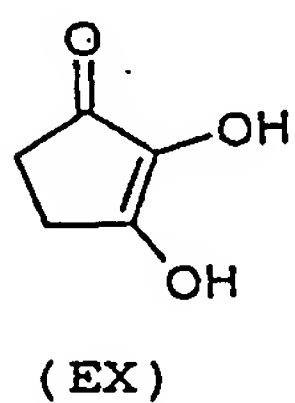
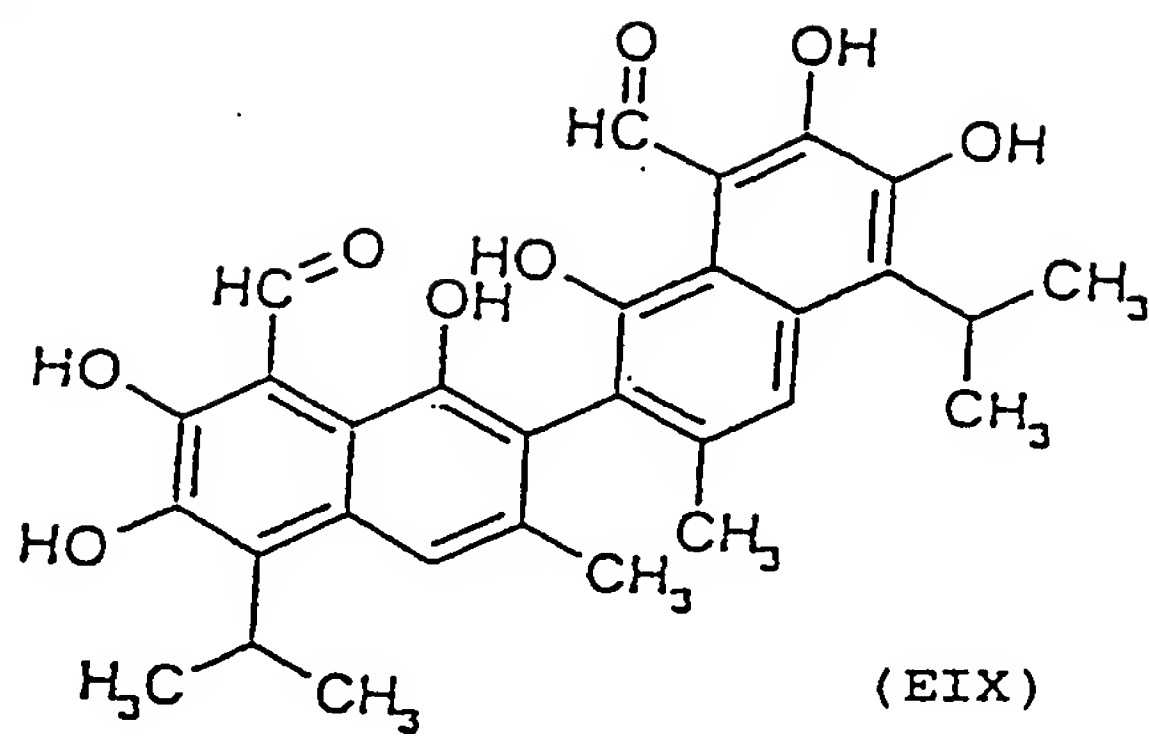
(EVI)

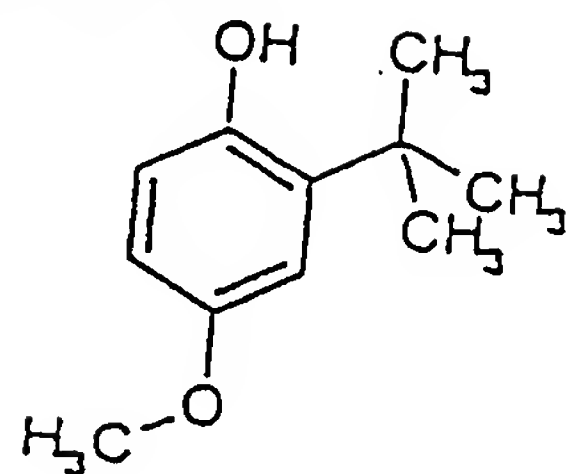


(EVII)

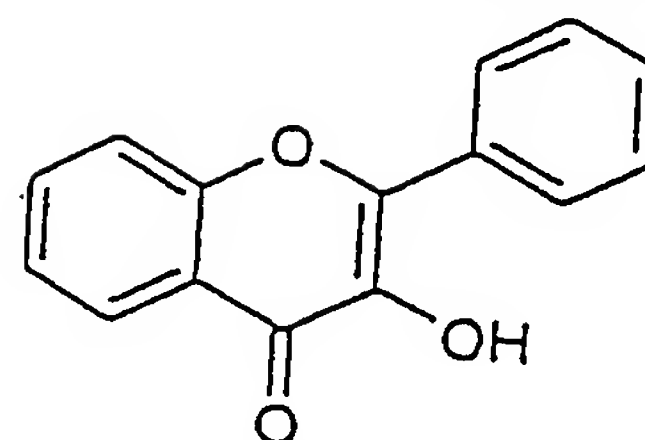


(EVIII)

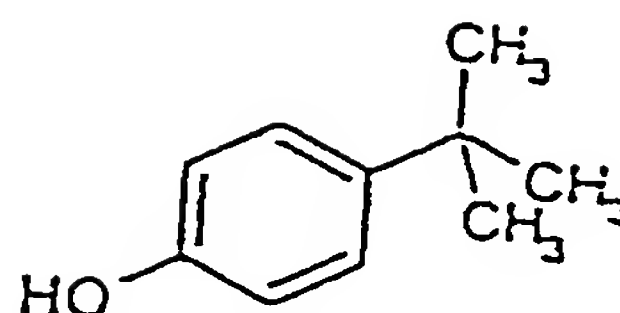




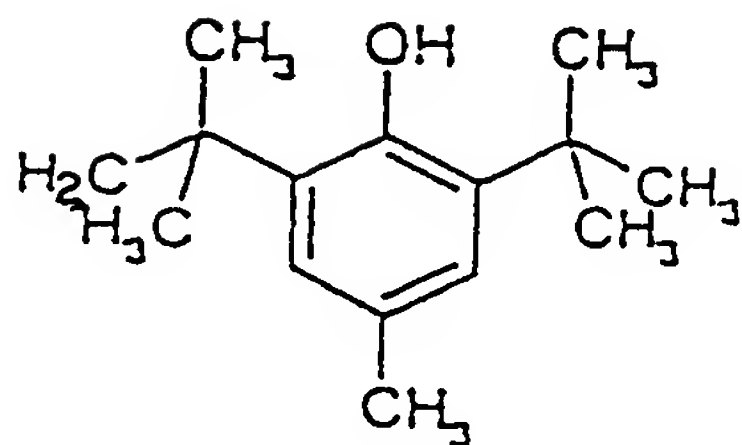
(EXVIII)



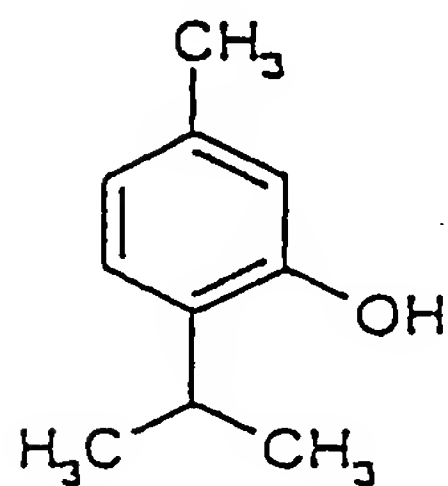
(EXIX)



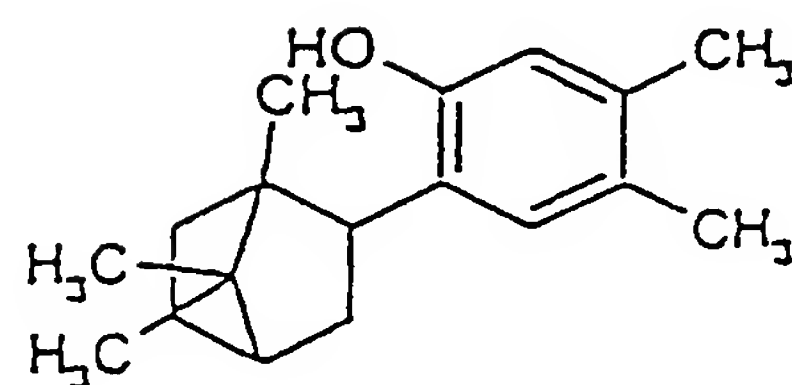
(EXXI)



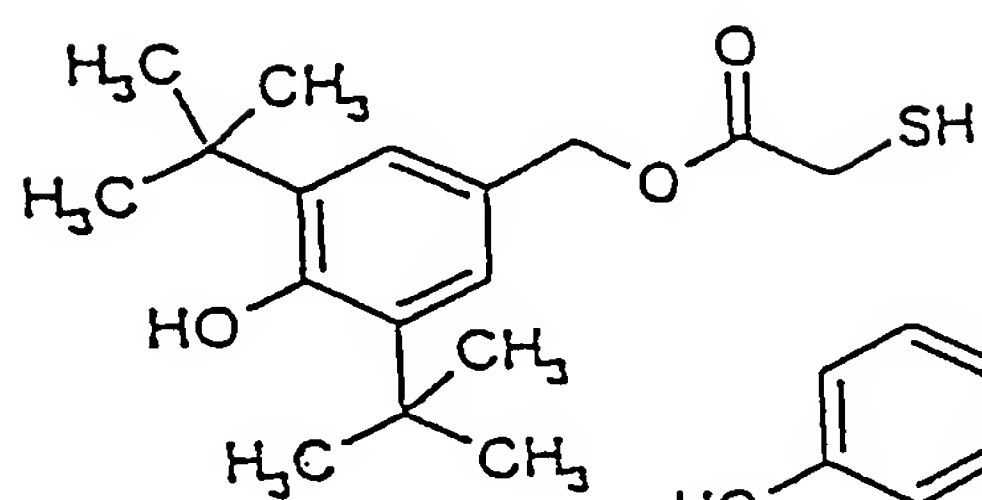
(EXX)



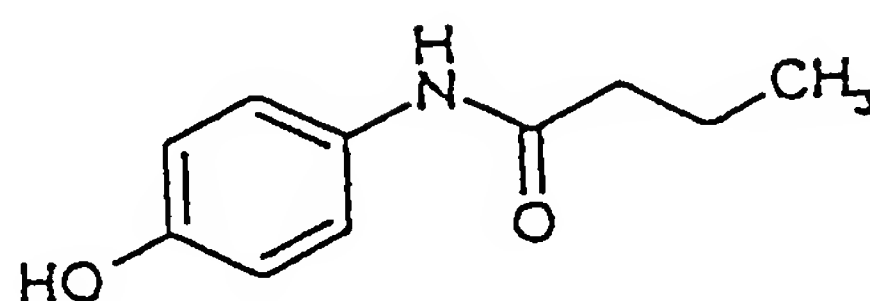
(EXXII)



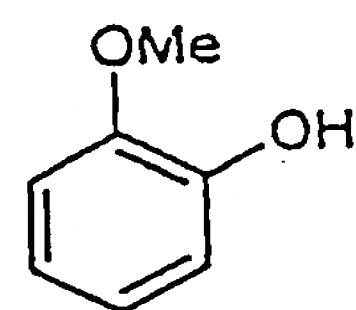
(EXXIII)



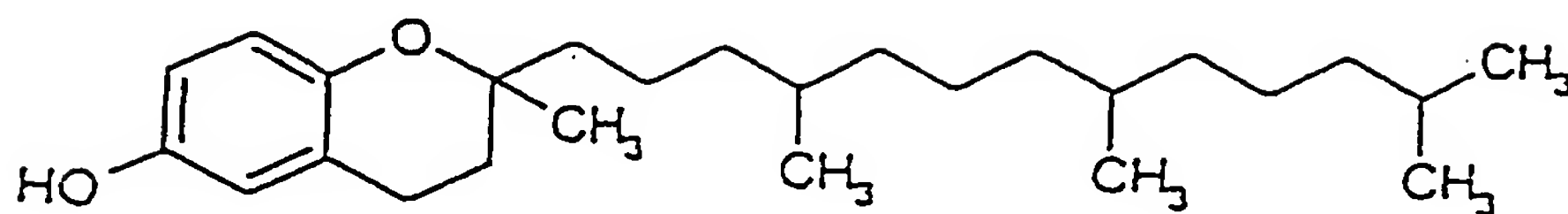
(EXXIV)



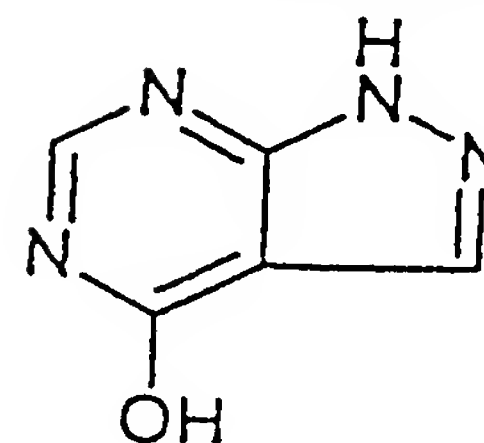
(EXXV)



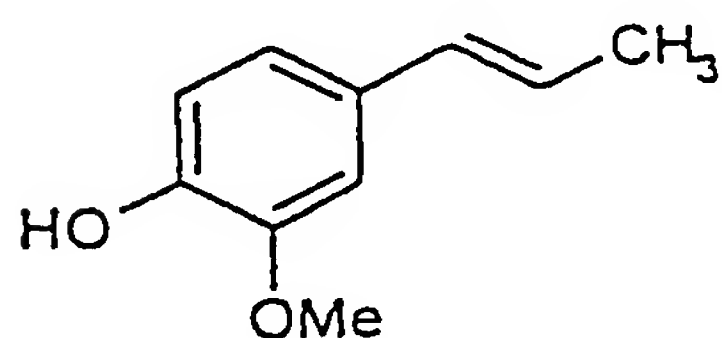
(EXXVI)



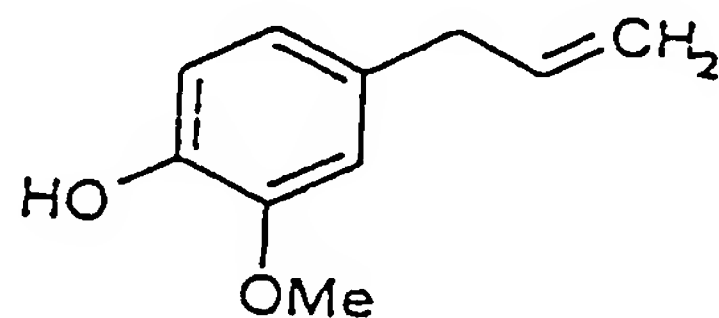
(EXXVII)



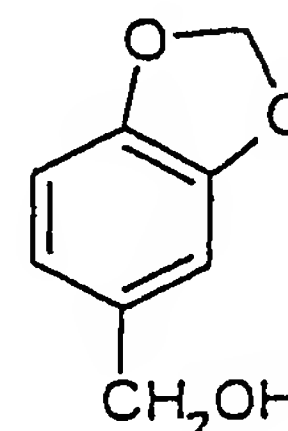
(EXXXI)



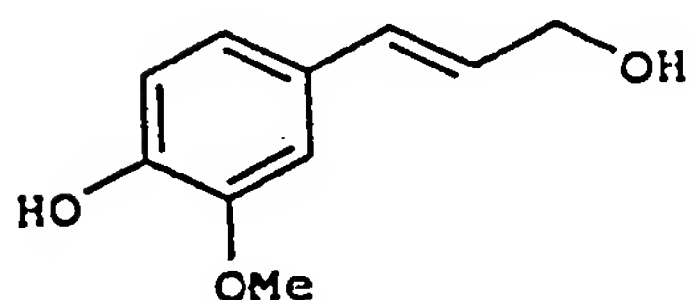
(EXXVIII)



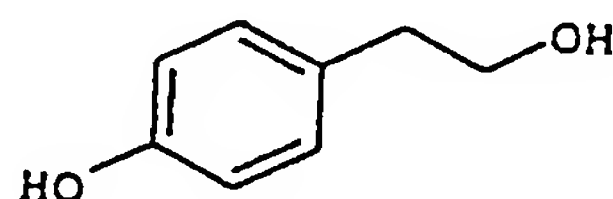
(EXXIX)



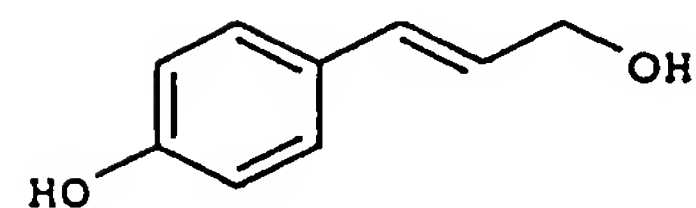
(EXXX)



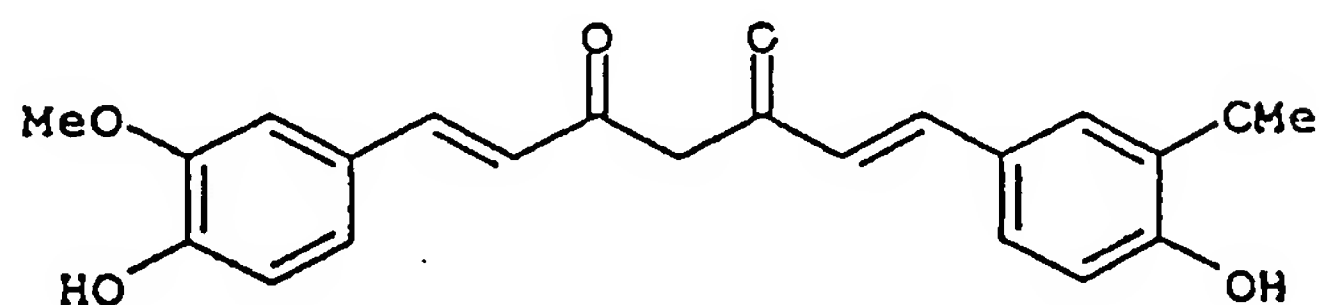
(EXXXII)



(EXXXIII)

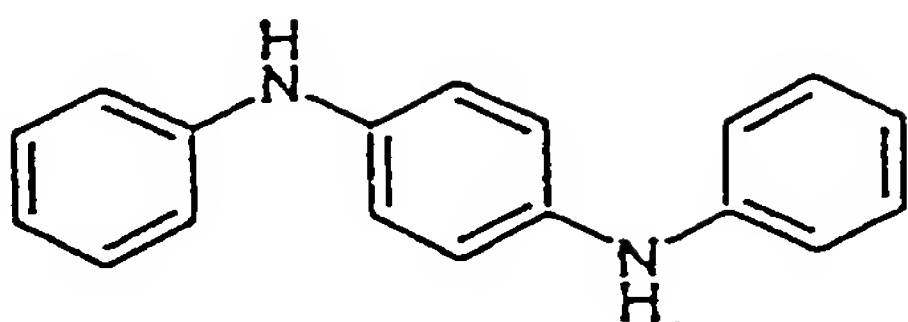


(EXXXIV)

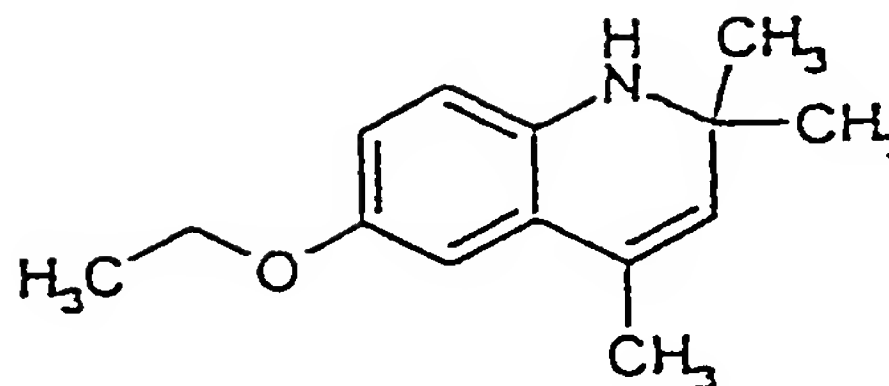


(EXXXV)

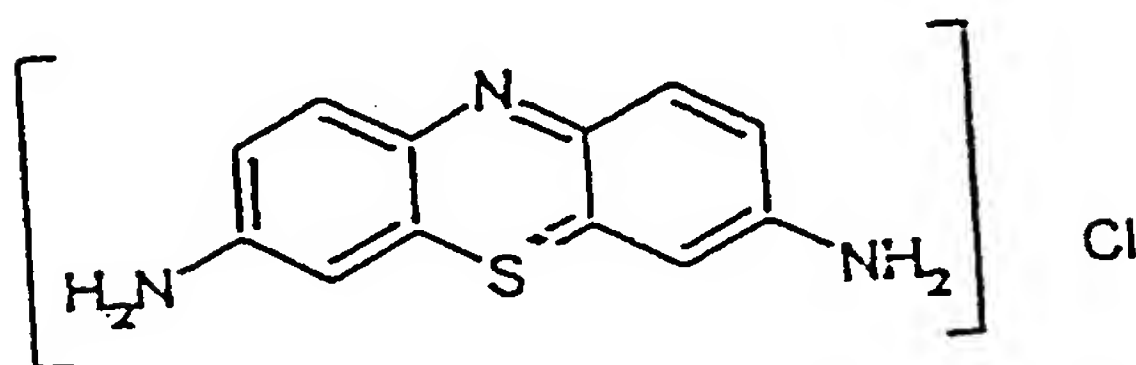
aromatic and heterocyclic amines, selected from the following: N, N'-diphenyl-p-phenylenediamine (MI), ethoxyquin (MII), thionine (MIII), hydroxyurea (M-IV):



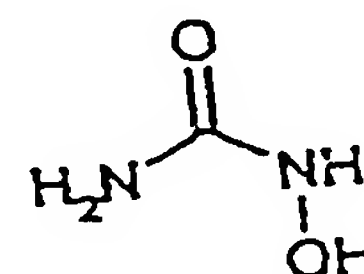
(MI)



(MII)

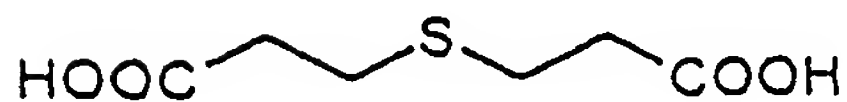


(MIII)

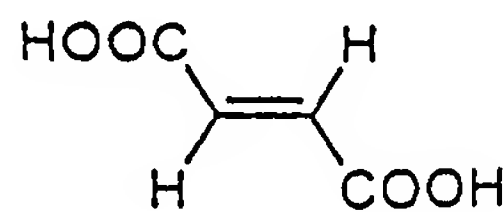


(MIV)

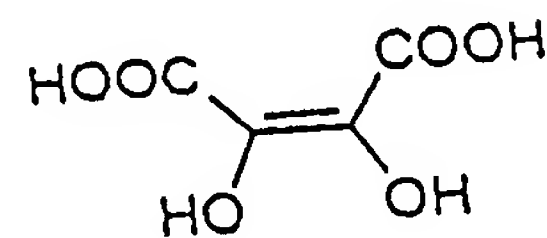
- Compounds containing at least a free acid function, selected from the following: 3,3'-thiodipropionic acid (NI), fumaric acid (NII), dihydroxymaleic acid (NIII), thiocetic acid (NIV), edetic acid (NV), bilirubin (NVI), 3,4-methylenedioxcinnamic acid (NVII), piperonylic acid (NVIII):



(NI)



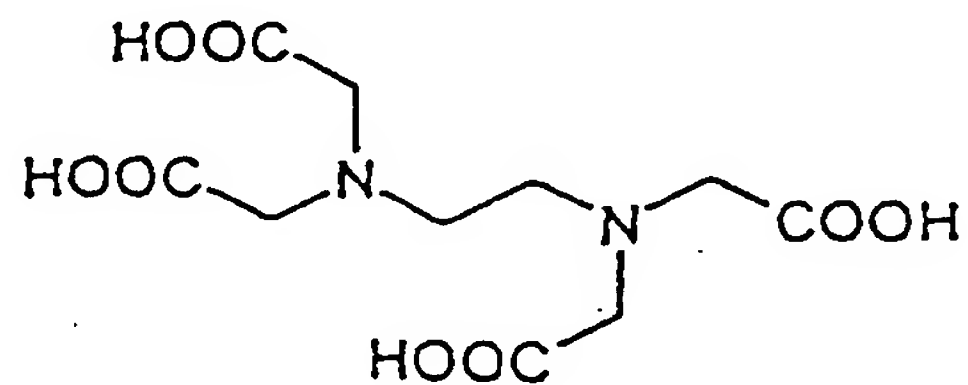
(NII)



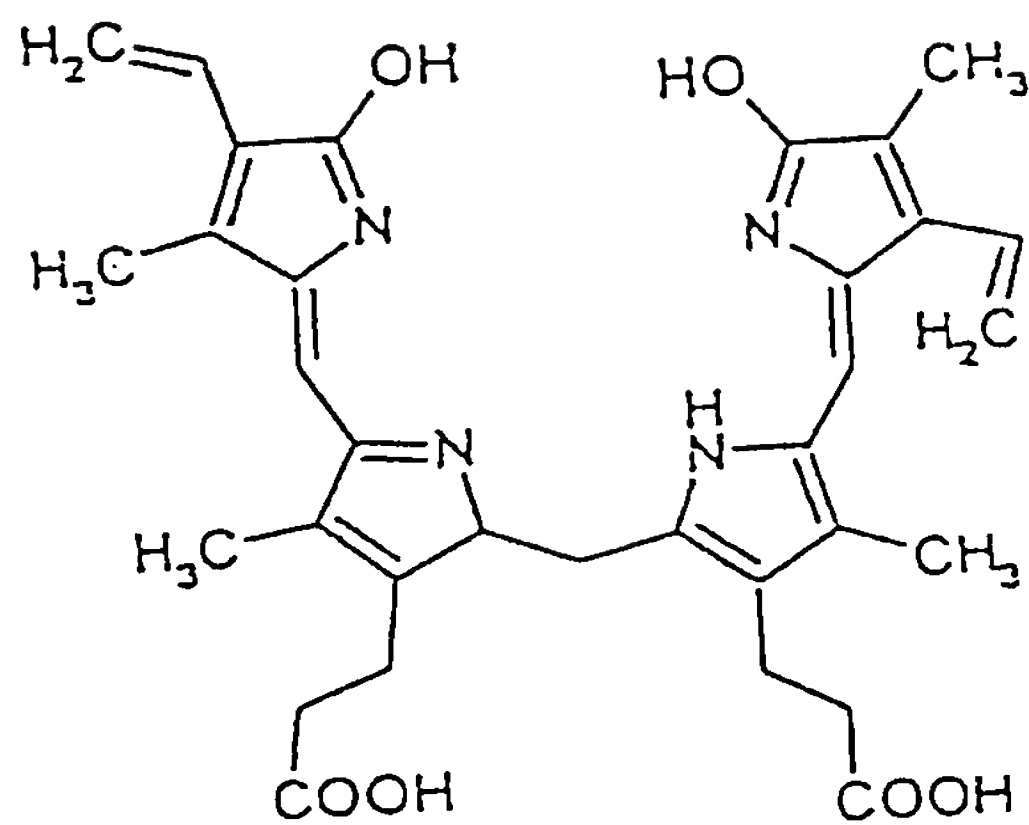
(NIII)



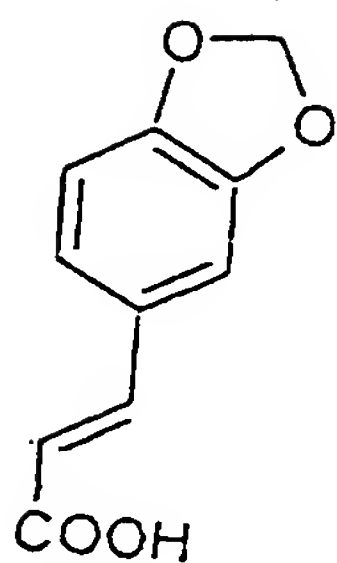
(NIV)



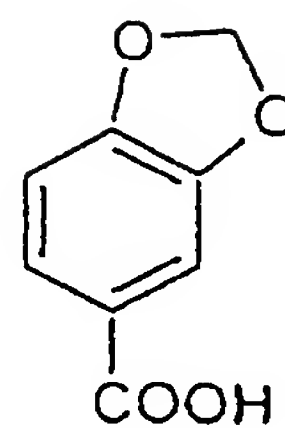
(NV)



(NVI)

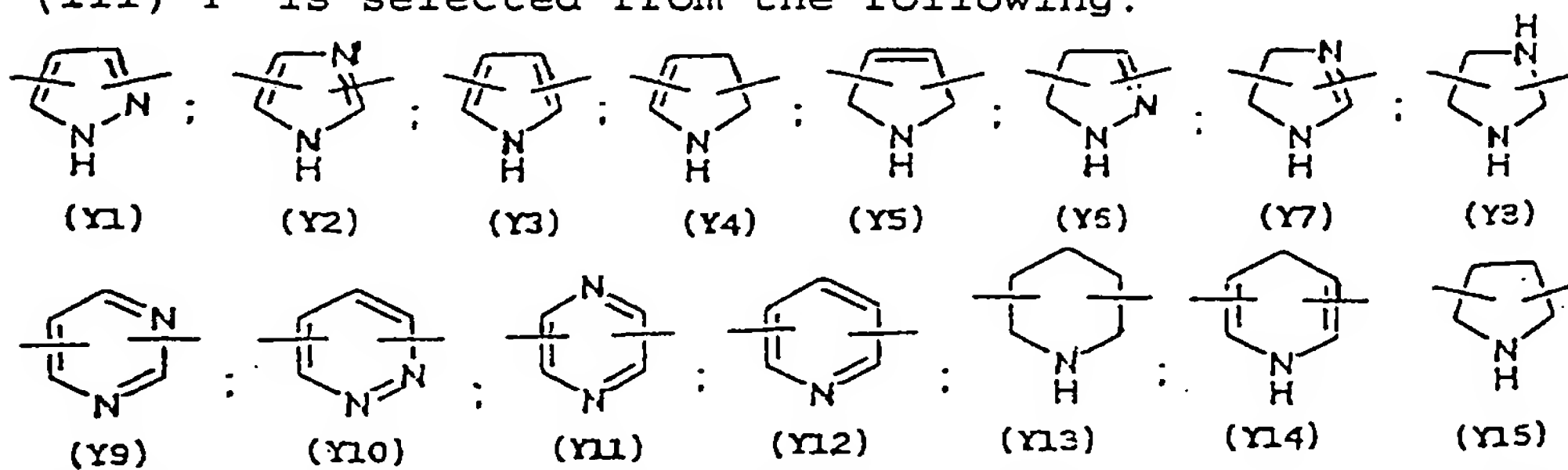


(NVII)



(NVIII)

3. Compounds according to claims 1-2, wherein in formula (III) Y^3 is selected from the following:



4. Compounds according to claims 1-2, wherein $Y' = -R'O-$ and

$Y = -R'O-$, R' has 1-6 carbon atoms.

5. Compounds according to claims 1-4 wherein the precursor drugs of the compounds of formula (I) and (II) are selected from the following: anti-inflammatory, analgesic drugs, bronchodilators and drugs active on the cholinergic system, expectorant-mucolytic drugs, anti-asthmatic-antiallergic, antihistaminic drugs, ACE-inhibitors, beta-blockers, antithrombotic drugs, vasodilators, antidiabetic, antitumoral, antiulcer, antihyperlipidemic, antibiotic, antiviral drugs, bone reabsorption inhibitors, antidementia drugs.
6. Compounds according to claim 5, wherein the precursor drugs are selected from the following:
- anti-inflammatory drugs: aceclofenac, acemetacin, acetylsalicylic acid, 5-aminoacetylsalicylic acid, alclofenac, alminoprofen, amfenac, bendazac, bermoprofen, α -bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen, cinmetacin, clidanac, clopirac, sodium diclofenac, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, olsalazine, oxaceprol, oxaprozin, oxyphenbutazone, parsalmide, perisoxal, phenyl acetylsalicylate, pyrazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicilamide O-

acetic acid, salicylsulphuric acid, salsalate, sulindac, suprofen, suxibuzone, tenoxicam, tiaprofenic acid, tiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepirac, tomoxiprol; analgesic drugs: acetaminophen, acetaminosalol, aminochlorthenoxazin, acetylsalicylic 2-amino-4-picoline acid, acetylsalicylsalicylic acid, anileridine, benoxaprofen benzylmorphine, 5-bromosalicylic acetate acid, bucetin, buprenorphine, butorphanol, capsaicine, cinchophen, ciramadol, clometacin, clonixin, codeine, desomorphine, dezocine, dihydrocodeine, dihydromorphine, dimepheptanol, dipyroceryl, eptazocine, ethoxazene, ethylmorphine, eugenol, floctafenine, fosfosal, glafenine, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, p-lactophenetide, levorphanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nicomorphine, norlevorphanol, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, phenocoll, phenoperidine, phenylbutazone, phenylsalicylate, phenylramidol, salicin, salicylamide, tiorphan, tramadol, diacerein, actarit; bronchodilators and drugs active on the cholinergic system: acefylline, albuterol, bambuterol, bamifylline, bevonium methyl sulphate, bitolterol, carbuterol, clenbuterol, chlorprenaline, dioxethedrine, difylline, ephedrine, epinephrine, eprozinol, etafredine, ethylnorepinephrine, etofylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium bromide, isoetharine, isoprotenerol, mabuterol, metaproterenol, oxybutynin, oxitropium bromide, pirbuterol, procaterol, protokylol,

proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, 1-teobromineacetic acid, tiotropium bromide, tretoquinol, tulobuterol, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetrahydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: ambroxol, bromhexine, domiodol, erdosteine, guaiacol, guaifenesin, iodinated glycerol, letosteine, mesna, sobrerol, stepronin, terpin, tiopronin;

antiasthmatic/antiallergic antihistaminic drugs: acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam, chromoglycate, chromolyn, epinastine, fexofenadine, formoterol, histamine, hydroxyzine, levocabastine, lodoxamide, mabuterol, metron s, montelukast, nedocromil, repirinast, seratrodast, suplatast tosylate, terfenadine, tiaramide, urushiol, bromhexine;

ACE-inhibitors: alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, losartan, moveltipril, naphthopidil, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, urapidil;

beta-blockers: acebutolol, alprenolol, amosulalol, arotinolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, dilevalol, epanolol, esmolol, indenolol, labetalol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipridalol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol,

sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol;

antithrombotic and vasoactive drugs: acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betahistine, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, dalteparin, dipyridamole, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, heparin, lamifiban, midodrine, nadroparin, nicotinyll alcohol, nylidrin, ozagrel, perhexiline, phenylpropanolamine, prenylamine, pavaroline, reviparin sodium salt, ridogrel, suloctidil, tinofedrine, tinzaparin, triflusal, xanthinol niacinate;

antidiabetic drugs: acarbose, carbutamide, glibornuride glybuthiazol(e), miglitol, repaglinide, troglitazone, 1-butyl-3-metanyl-urea, tolrestat, nicotinamide;

antitumoral drugs: ancitabine, anthramycin, azacitidine, azaserine, 6-azauridine, bicalutamide, carubicin, carzinophilin, chlorambucil, chlorozotocin, cytarabine, daunorubicin, defosfamide, demecolcine, denopterin, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicin, droloxifene, edatrexate, eflornithine, enocitabine, epirubicin, epitiostanol, ethanidazole, etoposide, fenretinide, fludarabine, fluorouracil, gemcitabine, hexestrol, idarubicin, lonidamine, mannomustine, melphalan, menogaril, 6-mercaptopurine, methotrexate, mitobronitol, mitolactol, mitomycins, mitoxantrone, mopidamol, mycophenolic acid, ninopterin, nogalamycin,

paclitaxel, pentostatin, pirarubicin, piritrexim, plicamycin, podophyllic acid, porfimer sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, thiamiprine, thioguanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicin;

antiulcer drugs: ϵ -acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecabet, enprostil, esaprazole, irsogladine, misoprostol, omeprazole, ornoprostil, pantoprazole, plaunotol, rioprostil, rosaprostol, rotraxate, sofalcone, trimoprostil;

anti-hyperlipidemic drugs: atorvastatin, cilastatin, dermostatin, fluvastatin, lovastatin, mevastatin, nystatin, pentostatin, pepstatin, pravastatin sodium salt, simvastatin;

antibiotics: amdinocillin, amoxicillin, ampicillin, apalcillin, apicycline, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoylpas, benzyl penicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole,

ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephacetrile sodium, cephalixin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cephapirin sodium, cephradine, chloramphenicol, chlortetracycline, cinoxacin, cyprofloxacin, clavulanic acid, clometocillin, cloxacillin, cyclacillin, cycloserine, demeclocycline, dicloxacillin, epicillin, fenbecillin, flomoxef, floxacillin, hetacillin, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, meclocycline, meropenem, metampicillin, methacycline, methicillin sodium salt, mezlocillin, minocycline, moxalactam, mupirocin, myxin, negamycin, novobiocin, oxacillin, panipenem, penicillin G potassium salt, penicillin N, penicillin O, penicillin V, phenethicillin potassium salt, pipacycline, piperacillin, pirlimycin, porfiromycin, propicillin, quinacillin, ritipenem, rolitetracycline, sancycline, sedecamycin, spectinomycin, sulbactam, sulbenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidin, azithromycin, clarithromycin, dirithromycin, enviomycin, erythromycin, josamycin, midecamycin, miokamycin, oleandomycin, rifabutin, rifamide, rifamycin, rifaximin, rokita-mycin, spiramycin, troleandomycin, viomycin, virginiamycin;

amikacin, apramycin, arbekacin, dibekacin, dihydrostreptomycin, fortimicins, gentamicin, micronomicin, neomycin, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin; bacampicillin, cefcapene

pivoxil, cefpodoxime proxetil, panipenem, pivampicillin, pivcefalexin, sultamicillin, talampicillin;

carbomycin, clindamycin, lincomycin, mikamycin, rosaramicin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, flumequine, grepafloxacin, lomefloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rufloxacin, sparfloxacin, tosufloxacin, trovafloxacin, clomocycline, guamecycline, oxytetracycline, nifurpirinol, nifurprazine;

p-aminosalicylic acid, p-aminosalicylic acid hydrazide, clofazimine, deoxydihydrostreptomycin, ethambutol, glyconiazide, isoniazid, opiniazide, phenyl aminosalicylate, rifampin, rifapentine, salinazid, 4-4'-sulfynyldianiline,

acediasulfone, dapson, succisulfone, p-sulfanilylbenzyl amine, thiazolsulfone, acetyl sulfamethoxypyrazine, mafenide, 4'-(methylsulfamoyl)sulfanilanilide, salazosulfadimidine, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 2-p-sulfanilylanilinoethanol, N⁴-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine,

sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfisomidine, sulfisoxazole, 4-sulfanilamido salicylic acid; negamycin, carumonan, cloxyquin, nitroxoline, arginine, metronidazole;

antiviral drugs: acyclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, indanavir, kethoxal, lamivudine, MADU, penciclovir, podophyllotoxin, ribavirin, rimantadine, saquinavir, sorivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine;

bone reabsorption inhibitors: alendronic acid, butedronic acid, etidronic acid, oxydronic acid, pamidronic acid, risedronic acid;

antidementia drugs: amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

7. Compounds according to claims 5-6, wherein the precursor drugs are selected from the following:

anti-inflammatory drugs: acetylsalicylic acid, 5-aminoacetylsalicylic acid, carprofen, diclofenac sodium salt, diflunisal, etodolac, flufenamic acid, flunixin, flurbiprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, naproxen, niflumic acid, olsalazine, piroxicam, salsalate, sulindac, suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, tolmetin, zomepirac, tomoxiprol;

analgesic drugs: acetaminophen, acetylsalicylsalicylic

acid, benoxaprofen, buprenorphine, butorphanol, capsaicin, diacerein, dihydrocodeine, ethylmorphine, eugenol, phenylbutazone, meptazinol, morphine, nalbuphine, pentazocine, thiorphan, tramadol, actarit;

bronchodilators drugs and drugs active on the cholinergic system: albuterol, carbuterol, clenbuterol, difylline, etofylline, fenoterol, ipratropium bromide, metaproterenol, oxybutynin, pirbuterol, salmeterol, terbutaline, tiotropium bromide, zaprinast, cyclo-drine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetra hydro-pyridin-4-yl methyl)acetamide;

expectorant/mucolytic drugs: ambroxol, bromexine, guaia-col, sobrerol;

antiasthmatic/antiallergic antihistaminic drugs:

cetirizine, chromoglycate, histamine, levocabastine, lodoxamide, montelukast, terfenadine, bromexine;

ACE-inhibitors: captopril, enalapril, lisinopril, losartan, ramipril;

beta blockers: alprenolol, atenolol, bupranolol, labetalol, metipranolol, metoprolol, pindolol, propranolol, timolol;

antithrombotic and vasoactive drugs: acetylsalicylic acid, acetorphan, argatroban, clopidogrel, dalteparin, dipyridamole, enoxaparin, heparin, iloprost, midodrine, ozagrel, phenylpropanolamine, trifusal;

antidiabetic drugs: tolrestat, nicotinamide;

antitumoral drugs: anthramycin, daunorubicin, doxorubicin, epirubicin, fluorouracyl, methotrexate, vinblastine;

antiulcer drugs: cimetidine, omeprazole, pantoprazole;

antihyperlipidemic drugs: lovastatin, pravastatin sodium salt, simvastatin;

antibiotics drugs: amoxicillin, ampicillin, aztreonam, biapenem, carbenecillin, cefaclor, cefadroxil, cefamandole, cefatrizine, cefoxitin, clavulanic acid, dicloxacillin, imipenem, meclocycline, methacycline, moxalactam, panipenem, sulbactam, azithromycin, erythromycin, josamycin, miokamycin, rifabutine, rifamide, rifamycin, gentamicin, paromomycin, sisomicin, bacampicillin, carbomycin, clindamycin, ciprofloxacin, clinafloxacin, difloxacin, enrofloxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pipemidic acid, apicycline, clomocycline, oxytetracycline, nifurpirinol, nifurprazine, isoniazid, rifampin, rifapentine, dapsone, thiazolsulfone, sulfamethoxazole, sulfamoxole, metronidazole, arginine;

antiviral drugs: aciclovir, famciclovir, ganciclovir, penciclovir, ribavirin, vidarabine, zidovudine;

bone resorption inhibitors: alendronic acid, etidronic acid, pamidronic acid.

8. Compounds or salts, or their compositions according to claims 1-7 for use as drugs.
9. Use of compounds or salts, or compositions thereof according to claims 1-7 for the preparation of drugs for the therapeutic stress-oxidative application.
10. Pharmaceutical formulations containing as active principle the compounds or their salts of claims 1-7.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07C 219/06, 219/22, 219/24, C07D 219/10, 233/64, 277/06, 277/14, 309/30, 401/12, 405/14, 417/06, 473/18, 495/04, 499/68, C07F 9/38, C07H 15/252, C07K 5/02, A61K 31/21	A2	(11) International Publication Number: WO 00/61541 (43) International Publication Date: 19 October 2000 (19.10.00)
(21) International Application Number: PCT/EP00/03239 (22) International Filing Date: 11 April 2000 (11.04.00) (30) Priority Data: MI99A000752 13 April 1999 (13.04.99) IT (71) Applicant (for all designated States except US): NICOX S.A. [FR/FR]; 45, Avenue Kléber, F-75116 Paris (FR). (72) Inventor; and (75) Inventor/Applicant (for US only): DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I-20052 Monza (IT). (74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni, 2, I-20129 Milano (IT).		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: PHARMACEUTICAL COMPOUNDS <div style="display: flex; justify-content: space-around; align-items: center;"><div style="text-align: center;">$A-(B)_{b0}-C-N(O)_s \quad (I)$</div><div style="text-align: center;">$\begin{array}{c} A-C_1-B_1 \\ \\ N(O)_s \end{array} \quad (II)$</div></div> (57) Abstract Compounds or their salts having general formulas (I) and (II) wherein: s = is an integer equal to 1 or 2, preferably s = 2; b0 = 0 or 1; A is the radical of a drug and is such as to meet the pharmacological tests reported in the description, C and C ₁ are two bivalent radicals. The precursors of the radicals B and B ₁ are such as to meet the pharmacological test reported in the description.		

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"PHARMACEUTICAL COMPOUNDS"

* * * * *

The present invention relates to new drugs for systemic use and non systemic use, and the composition thereof, to be used in oxidative stress and/or endothelial dysfunctions cases.

By oxidative stress it is meant the generation of free radicals or radicalic compounds, which causes injury both of the cell and that of the surrounding tissue (Pathophysiology: the biological basis for disease in adults and children, McCance & Huether 1998 pages 48-54).

By endothelial dysfunctions it is meant those relating to the vasal endothelium. The damage of the vasal endothelium is known as one of those important events that can cause a series of pathological processes affecting various organs and body apparatuses, as described hereinafter (Pathophysiology: The biological basis for disease in adults and children, McCance & Huether 1998 page 1025).

As known, the oxidative stress and/or the endothelial dysfunctions are associated to various pathologies as reported hereinafter. The oxidative stress can also be caused by toxicity of a great variety of drugs, which significantly affects their performances.

Said pathological events are of a chronic, debilitating character and are very often typical of the elderly. As already

said, in said pathological conditions the drugs used show a remarkably worsened performance.

Examples of pathological situations caused by the oxidative stress and/or by the endothelial dysfunctions, or present in elderly, are the following:

- For the cardiovascular system: myocardial and vascular ischaemia in general, hypertension, stroke, arteriosclerosis, etc.
- For the connective tissue: rheumatoid arthritis and connected inflammatory diseases, etc.
- For the pulmonary system: asthma and connected inflammatory diseases, etc.
- For the gastrointestinal system: ulcerative and non ulcerative dyspepsias, intestinal inflammatory diseases, etc.
- For the central nervous system: Alzheimer disease, etc.
- For the urogenital system: impotence, incontinence.
- For the cutaneous system: eczema, neurodermatitis, acne.
- The infective diseases in general (ref.: Schwarz-KB, Brady "Oxidative stress during viral infection: A review" Free radical Biol. Med. 21/5, 641-649 1996).

Further the ageing process can be considered as a true pathologic condition (ref. Pathophysiology: the biological basis for disease in adults and children, pages 71-77).

The known drugs when administered to patients having

pathologies associated to oxidative stress and/or endothelial dysfunctions, show a lower activity and/or higher toxicity.

This happens for example for drugs such as the antiinflammatory, cardiovascular drugs, respiratory apparatus drugs, central nervous system drugs, bone system drugs, antibiotics, urogenital, endocrine drugs, etc.

Drug research is directed to find new molecules having an improved therapeutic index (efficacy/toxicity ratio) or a lower risk/benefit ratio, also for pathological conditions as those above mentioned, wherein the therapeutic index of a great number of drugs results lowered. In fact in the above mentioned conditions of oxidative stress and/or endothelial dysfunctions, many drugs show a lower activity and/or higher toxicity.

For instance antiinflammatory drugs, such as NSAIDs and anticolitic drugs, such as 5-aminosalicylic acid and its derivatives, show the following drawbacks. NSAIDs result toxic particularly when the organism is debilitated or affected by morbid conditions associated to oxidative stress. Said conditions are for example the following: age, pre-existing ulcer, pre-existing gastric bleeding, debilitating chronic diseases such as in particular those affecting cardiovascular, renal apparatuses, the haematic crisis, etc. ("Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving non-steroidal anti-inflammatory drugs. A randomized, double blind, placebo-controlled trial."

F.E. Silverstein et Al., Ann. Intern. Med. 123/4, 241-9, 1995; Martindale 31a ed. 1996, pag. 73, Current Medical Diagnosis and Treatment 1998, pages 431 and 794).

The administration of anti-inflammatory drugs to patients in the above mentioned pathological conditions can be made only at doses lower than those used in therapy in order to avoid remarkable toxicity phenomena. Thus anti-inflammatory activity results poor.

Beta-blockers, used for the angina, hypertension and cardiac arrhythmia treatment, show side effects towards the respiratory apparatus (dyspnoea, bronchoconstriction), and therefore they can cause problems in patients affected by pathologies to said organs (asthma, bronchitis). Therefore beta-blockers further worsen respiratory diseases such as asthma. Therefore in asthmatic patients doses of said drugs must be used reduced in order not to jeopardize even more the respiratory functionality. Thus the efficacy of the beta-blockers results very reduced.

Antithrombotics, such as for example dipyridamole, aspirin, etc., used for the prophylaxis of thrombotic phenomena, have the same drawbacks. In patients affected by pathologies connected to oxidative stress and/or endothelial dysfunctions, the therapeutic action or the tolerability of these drugs, as in the case of aspirin, is greatly reduced.

Bronchodilators for example salbutamol, etc., are used in

the asthma and bronchitis treatment and drugs active on the cholinergic system are used in pathologies such as urinary incontinence. Their administration can produce similar side effects affecting the cardiovascular apparatus, causing problems both to cardiopathic and to hypertensive patients. Cardiopathies and hypertension are pathologies associated, as above said, to the oxidative stress and/or endothelial dysfunctions. Also these drugs show the same drawbacks as those above mentioned.

Expectorant and mucolytic drugs, which are used in the therapy of inflammatory states of the respiratory organs, show drawbacks in patients affected by the above described conditions. Their administration can give rise to heartburn and gastric irritability, particularly in the elderly.

Bone resorption inhibitors, such as diphosphonates (for example alendronate, etc.) are drugs showing high gastrointestinal toxicity. Therefore also these drugs can show the same drawbacks as those above mentioned.

Phosphodiesterase inhibitors, such as for example sildenafil, zaprinast, used in the cardiovascular and respiratory system diseases, are characterized by similar problems as to tolerability and/or efficacy in the mentioned pathological conditions of oxidative stress and/or endothelial dysfunctions.

Antiallergic drugs, for example cetirizine, montelukast,

etc. show similar problems in the mentioned pathological conditions, particularly for that it concerns their efficacy.

Anti-angiotensin drugs, f.i. ACE-inhibitors, for example enalapril, captopril, etc., and receptor inhibitors, for example losartan, etc., are used in the cardiovascular disease treatment. Their drawback is to give side effects to the respiratory apparatus (i.e. cough, etc.) in the above mentioned pathological conditions.

Antidiabetic drugs, both of the insulin-sensitizing and of hypoglycaemizing type, such as for example sulphonylureas, tolbutamide, glypiride, glyclazide, glyburide, nicotinamide etc., are ineffective in the prophylaxis of diabetic complications. Their administration can give side effects, such as for example gastric lesions. These phenomena become more intense in the pathological conditions above mentioned.

Antibiotics, for example ampicillin, clarithromycin, etc., and antiviral drugs, acyclovir, etc., show problems as regards their tolerability, for example they cause gastro-intestinal irritability.

Antitumoral drugs, for example doxorubicine, daunorubicin, cisplatinum, etc., have high toxicity, towards different organs, among which are stomach and intestine. Said toxicity is further worsened in the above mentioned pathologies of oxidative stress and/or endothelial dysfunctions.

Antidementia drugs for example nicotine and colino-

mimetics, are characterized by a poor tolerability especially in the above mentioned pathologies.

The need was felt to have available drugs showing an improved therapeutic performance, i.e. endowed both of a lower toxicity and/or higher efficacy, so that they could be administered to patients in morbid conditions of oxidative stress and/or endothelial dysfunctions, without showing the drawbacks of the drugs of the prior art.

It has now surprisingly and unexpectedly found that the aforementioned problems evidenced the administration of drugs, to patients affected by oxidative stress and/or endothelial dysfunctions, or to the elderly in general, are solved by a novel class of drugs as described hereinafter.

An object of the invention are compounds or their salts having the following general formulas (I) and (II):



wherein:

s = is an integer equal to 1 or 2, preferably s = 2;

b₀ = 0 or 1;

A = R-T₁-, wherein

R is the drug radical and

T₁ = (CO)_t or (X)_t., wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when

$$t' = 1;$$

B = $-T_B-X_2-T_{BI}-$ wherein

T_B and T_{BI} are equal or different;

$T_B = (CO)$ when $t = 0$, $T_B = X$ when $t' = 0$, X being as above defined;

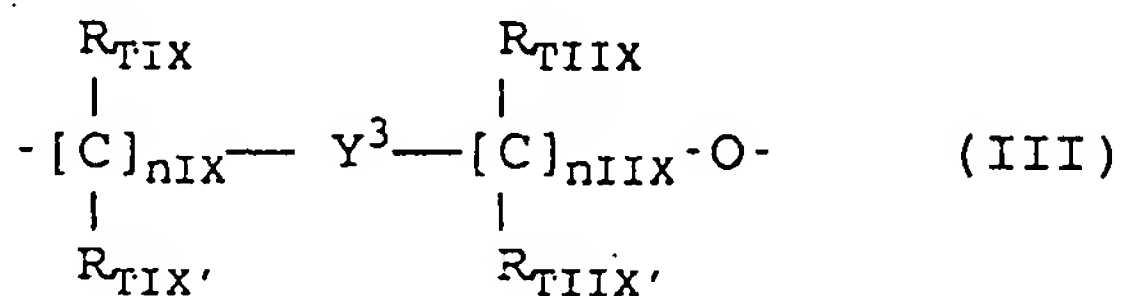
$T_{BI} = (CO)_{tx}$ or $(X)_{txx}$ wherein tx and txx have the 0 or 1 value; with the proviso that tx = 1 when txx = 0, and tx = 0 when txx = 1; X is as above defined;

X_2 is a bivalent bridging group as defined below;

C is the bivalent $-T_C-Y-$ radical, wherein

$T_C = (CO)$ when tx = 0, $T_C = X$ when txx = 0, X being as above defined;

Y is:



wherein:

nIX is an integer between 0 and 3, preferably 1;

nIIX is an integer between 1 and 3, preferably 1;

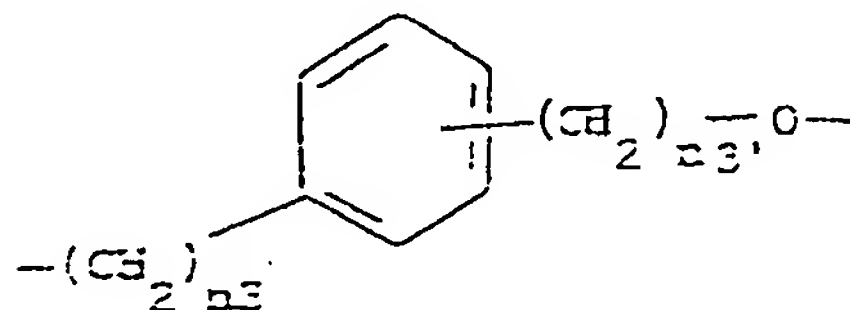
R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$, equal to or different from each other are H or a linear or branched C_1-C_4 alkyl; preferably R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$ are H.

Y^3 is a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen atom, preferably one or two nitrogen atoms, said ring

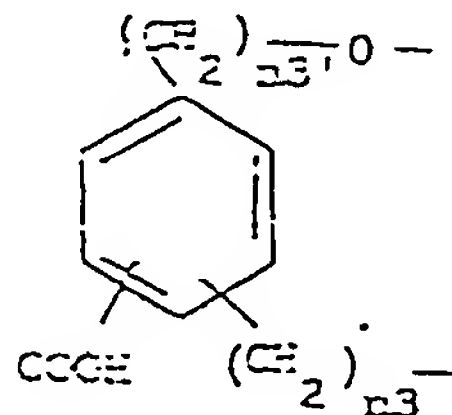
having 5 or 6 atoms.

or Y is Y₀, selected from the following:

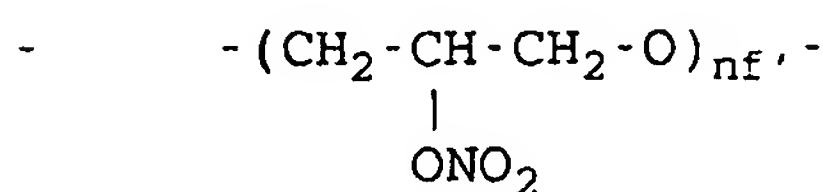
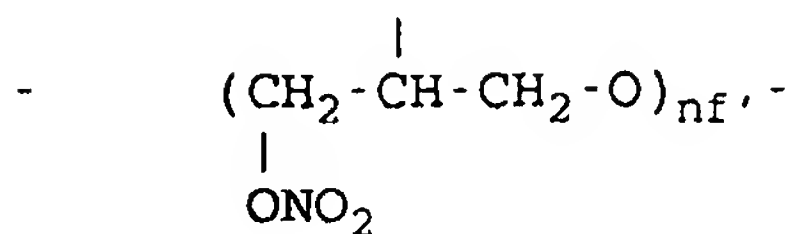
- an alkyleneoxy group R'O wherein R' is linear or branched when possible C₁-C₂₀, preferably having from 1 to 6 carbon atoms, most preferably 2-4, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be replaced by heteroatoms, the ring can have side chains of R' type, R' being as above defined; or



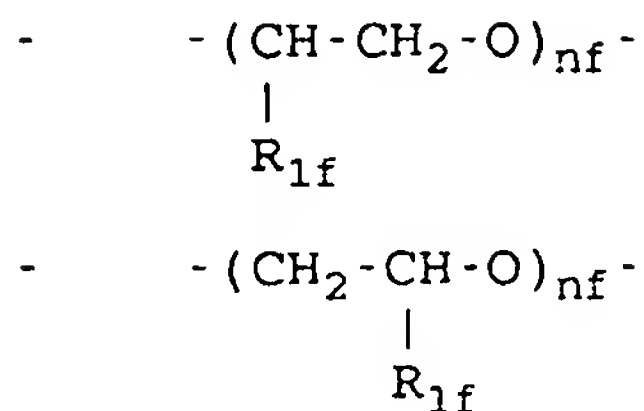
wherein n₃ is an integer from 0 to 3 and n₃' is an integer from 1 to 3;



wherein n₃ and n₃' have the above mentioned meaning



wherein nf' is an integer from 1 to 6 preferably from 1 to 4;



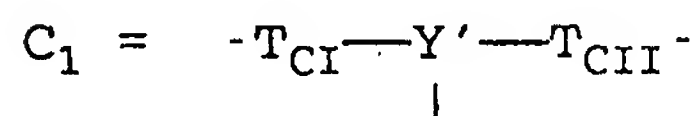
wherein $\text{R}_{1f} = \text{H}, \text{CH}_3$ and nf is an integer from 1 to 6; preferably from 1 to 4;

preferably $\text{Y} = -\text{Y}_0 = \text{R}'\text{O}-$ wherein R' is as above defined;

preferably R' is a $\text{C}_1\text{-C}_6$ alkyl;



wherein:

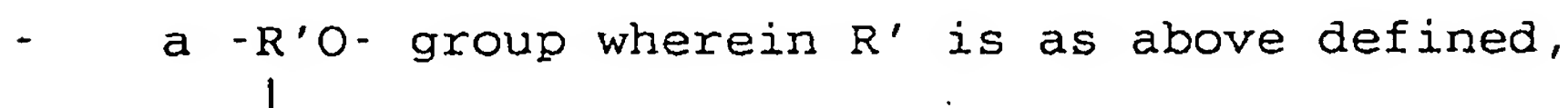


wherein T_{CI} and T_{CII} are equal or different,

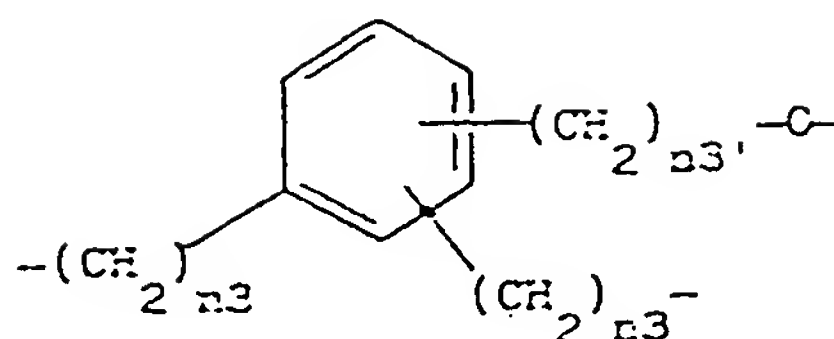
$\text{T}_{\text{CI}} = (\text{CO})$ when $t = 0$, $\text{T}_{\text{CI}} = \text{X}$ when $t' = 0$, X being as above defined;

$\text{T}_{\text{CII}} = (\text{CO})_{t\text{I}}$ or $(\text{X})_{t\text{II}}$, wherein $t\text{I}$ and $t\text{II}$ have the 0 or 1 value; with the proviso that $t\text{I} = 1$ when $t\text{II} = 0$; $t\text{I} = 0$ when $t\text{II} = 1$; X is as above defined;

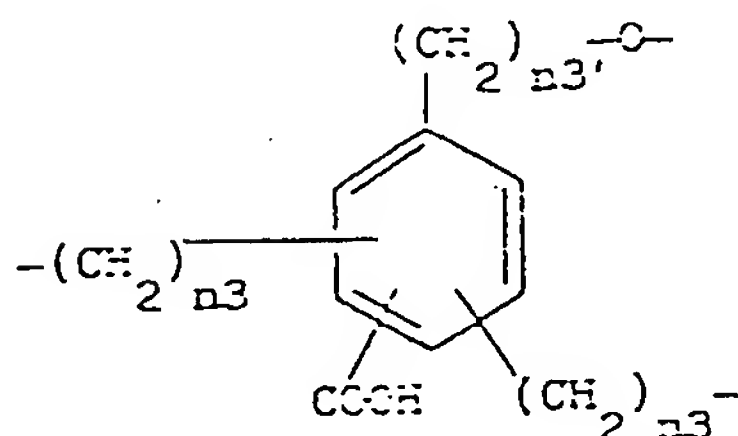
Y' is as Y above defined, but with three free valences instead of two, preferably:



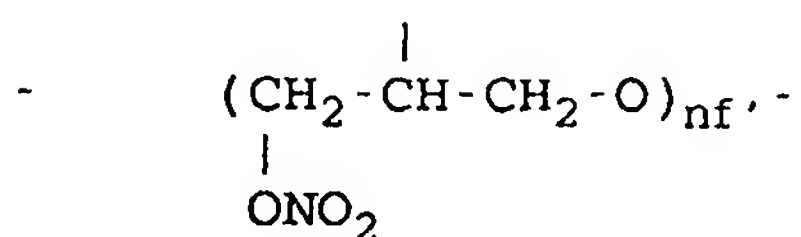
preferably an alkyl from 1 to 6 carbon atoms, most preferably 2-4; or



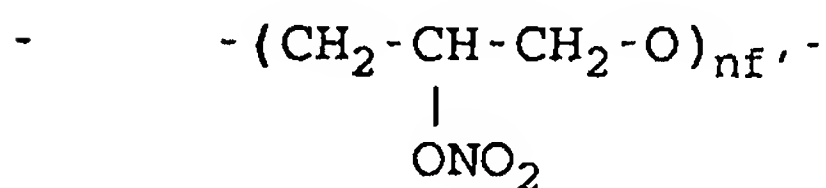
wherein n_3 is an integer from 0 to 3 and $n_{3'}$ is an integer from 1 to 3;



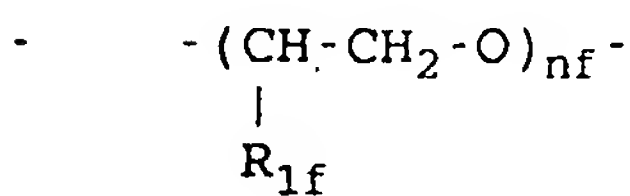
wherein n_3 and $n_{3'}$ have the above mentioned meaning;



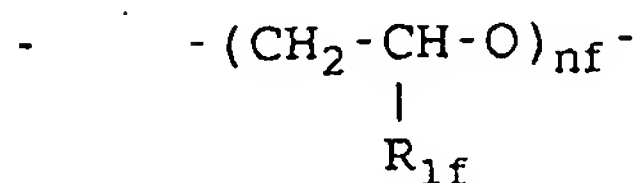
wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein nf' is an integer from 1 to 6 preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;

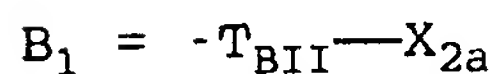


wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein $\text{R}_{1f} = \text{H}, \text{CH}_3$ and nf is an integer from 1 to 6; preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;

preferably $\text{Y}' = -\text{R}'\text{O}-$ wherein R' is a linear or branched C_2-C_4 , the oxygen which in Y' is covalently linked to the $-\text{N}(\text{O})_s$ group is at the end of the free bond indicated in C_1 formula;



wherein X_{2a} is a monovalent radical as defined below, $\text{T}_{\text{BII}} = (\text{CO})$ when $t\text{I} = 0$, $\text{T}_{\text{BII}} = \text{X}$ when $t\text{II} = 0$, X being as above defined;

- X_2 , bivalent radical, is such that the corresponding precursor of B: $-\text{T}_{\text{B}}-\text{X}_2-\text{T}_{\text{BI}}-$ meets test 5 but not test 4, precursor in which the T_{B} and T_{BI} free valences are each saturated with $-\text{OZ}$, $-\text{Z}$, or with $-\text{Z}^{\text{I}}-\text{N}-\text{Z}^{\text{II}}$, Z^{I} and Z^{II} being equal or different and have the Z values as defined below, depending on the fact that T_{B} and/or $\text{T}_{\text{BI}} = \text{CO}$ or X , in connection with the values of t , t' , tx and txx ;
- the precursor of C when $b_0 = 0$ is of $-\text{T}_{\text{C}}-\text{Y}-\text{H}$ type wherein the T_{C} free valence is saturated with $-\text{OZ}$, $-\text{Z}$, or with

$-Z^I-N-Z^{II}$, Z^I and Z^{II} being as above defined, meets
test 5;

- X_{2a} monovalent radical, such that the corresponding precursor of $B_1 - T_{BII} - X_{2a}$ meets test 5 but not test 4, precursor wherein the free valence of T_{BII} is saturated with $-OZ$, $-Z$ or with $-Z^I-N-Z^{II}$, Z^I and Z^{II} being equal or different and having the Z values as defined below, depending on the fact that $T_{BII} = CO$ or X , in connection with the values of tI and tII ;

- the drug $A = R - T_1 -$, wherein the free valence is saturated as indicated hereinafter:

- when $t' = 0$ with:

- $O-Z$ wherein $Z = H$ or R_{1a} , R_{1a} being a linear or when possible branched C_1-C_{10} alkyl, preferably C_1-C_5 , or with
- Z^I-N-Z^{II} , Z^I and Z^{II} being as above defined,

- when $t = 0$ with $-Z$, wherein Z is as above defined, with the proviso that the drug is not a steroid, is such as to meet at least one of tests 1-3;

- wherein test 1 (NEM) is a test in vivo carried out on four groups of rats (each formed by 10 rats), the controls (two groups) and the treated (two groups) of which one group of the controls and one group of the treated respectively are administered with one dose of 25 mg/kg s.c. of N-ethylmaleimide (NEM), the controls being treated with the carrier and the

treated groups with the carrier + the drug of formula $A = R-T_1$ - wherein the free valence is saturated as above indicated, administering the drug at a dose equivalent to the maximum one tolerated by the rats that did not receive NEM, i.e. the highest dose administrable to the animal at which there is no manifest toxicity, i.e. such as to be symptomatologically observable; the drug complies with test 1, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in the group treated with NEM + carrier + drug are observed gastrointestinal damages greater than those of the group treated with the carrier, or of the group treated with the carrier + drug, or of the group treated with the carrier + NEM;

- wherein test 2 (CIP) is a test in vitro wherein human endothelial cells from the umbilical vein are harvested under standard conditions, then divided into two groups (each group replicated five times), of which one is treated with a mixture of the drug 10^{-4} M concentration in the culture medium, the other group with the carrier; then cumene hydroperoxide (CIP) having a 5 mM concentration in the culture medium is added to each of the two groups; the drug meets test 2, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), if a statistically significant inhibition of the apoptosis (cellular damage) induced by CIP is not obtained

with $p < 0.01$ with respect to the group treated with the carrier and CIP;

wherein test 3 (L-NAME) is a test in vivo carried out on four groups of rats (each group formed by 10 rats) for 4 weeks and receiving drinking water, the controls (two groups) and the treated (two groups), of which one group of the controls and of the treated respectively receives in the above 4 weeks drinking water added of N- ω -nitro-L-arginine methyl ester (L-NAME) at a concentration of 400 mg/litre, the controls in the 4 weeks being administered with the carrier and the treated in the 4 weeks with the carrier + the drug, administering the carrier or the drug + carrier once a day, the drug being administered at the maximum dose tolerated by the group of rats not pretreated with L-NAME, i.e., the highest dose administrable to animals at which no manifest toxicity appears, i.e. such as to be symptomatologically observable; after the said 4 weeks, the water supply is stopped for 24 hours and then sacrificed, determining the blood pressure 1 hour before sacrifice, and after sacrifice of the rats determining the plasma glutamic pyruvic transaminase (GPT) after sacrifice, and examining the gastric tissue; the drug meets test 3, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when in the group of rats treated with L-NAME + carrier + drug, greater hepatic damages (determined as higher values of GPT) and/or gastric and/or cardiovascular damages (determined as

higher values of blood-pressure) are found in comparison in comparison respectively with the group treated with the carrier alone, or with the group treated with the carrier + drug, or with the group treated with the carrier + L-NAME;

wherein test 4, which must not be met by the precursors of B or B₁ with the free valences saturated as above defined, is the following: it is an analytical determination carried out by adding portions of methanol solutions of the precursor of B or B₁ at a 10⁻⁴ M concentration, to a methanol solution of DPPH (2,2-diphenyl-1-picryl hydrazyl - free radical); after having maintained the solution at room temperature away from light for 30 minutes, it is read the absorbance at the wave length of 517 nm of the test solution and of a solution containing only DPPH in the same amount as in the test solution; and then the inhibition induced by the precursor towards the radical production by DPPH is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the test compound + DPPH and that of the solution containing only DPPH.

The criterium for acceptance of the compounds according to this test is the following: test 4 is met by precursor compounds if the inhibition percentage as above defined is higher than or equal to 50%; the precursor of B or B₁ must not meet test 4;

wherein test 5 is the following: it is an analytical determination carried out by adding aliquots of 10^{-4} M methanol solutions of the precursor of B or B₁ or of C = -T_C-Y-H, having the free valence saturated as above indicated, to a solution formed by admixing a 2 mM solution of desoxyribose in water with 100 mM of phosphate buffer and 1 mM of the salt Fe^{II}(NH₄)₂(SO₄)₂; after having thermostatted the solution at 37°C for one hour, are added, in the order, aliquots of aqueous solutions of trichloroacetic acid 2.8% and of thiobarbituric acid 0.5 M, heating is effected at 100°C for 15 minutes and the absorbance of the solutions is then read at 532 nm; the inhibition induced by the precursor of B or B₁ or C = -T_C-Y-H in the confront of radical production by Fe^{II} is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound and the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage as above defined of the precursor of B or B₁ or C = -T_C-Y-H is higher than or equal to 50%;

provided that in the compounds of formula (I) the following drugs under the following conditions are excluded:

- when bo = 0 and C = -T_C-Y₀-, with the free valence of Y₀ saturated as above indicated, s = 2, the drug of formula A =

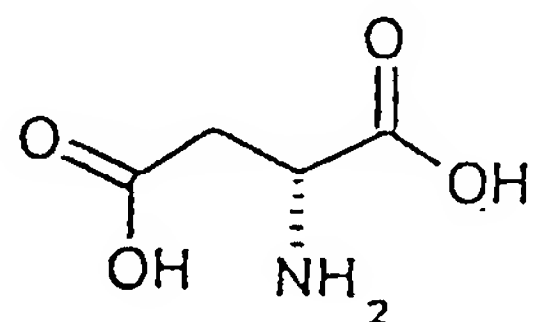
$R-T_1-$, as above defined, has not to belong to the following classes: drugs for use in incontinence, antithrombotic drugs (ACE-inhibitors), prostaglandins;

when $b_0 = 0$ and $C = -T_C-Y-$, with the free valence of Y saturated as above indicated, and $s = 2$, the drugs of formula $A = R-T_1-$ belonging to the class of non steroid antiinflammatory drugs.

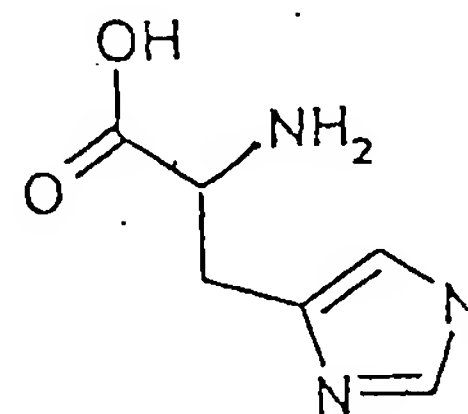
The drugs of the proviso to be excluded, as said, are the following: drugs for use in incontinence as described in the patent application WO 98/09948, antithrombotic drugs (ACE inhibitors) as described in the patent application WO 98/21193, prostaglandin derivatives as described in the patent application WO 98/58910. There are excluded also non steroid antiinflammatory (NSAIDs) as described in WO 95/30641, WO 94/12463, WO 95/09831 respectively.

Preferably the precursor compound of B or B_1 (precursor of the X_2 or X_{2a} radical in the formulas (I) and (II) respectively), is selected from the following classes of compounds:

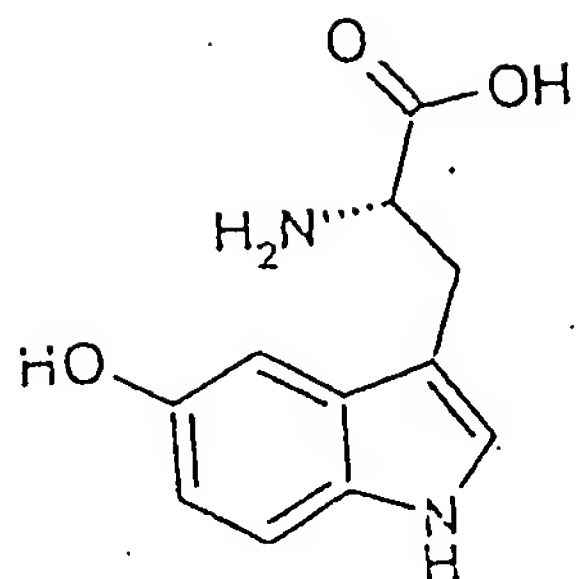
- Aminoacids: aspartic acid (PI), histidine (PII), 5-hydroxytryptophan (PIII), 4-thiazolidincarboxylic acid (PIV), 2-oxo-4-thiazolidincarboxylic acid (PV)



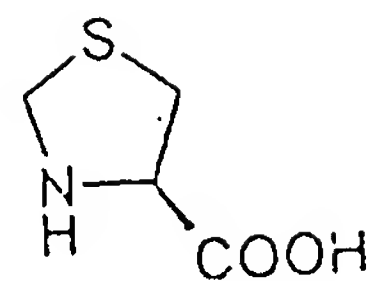
(PI)



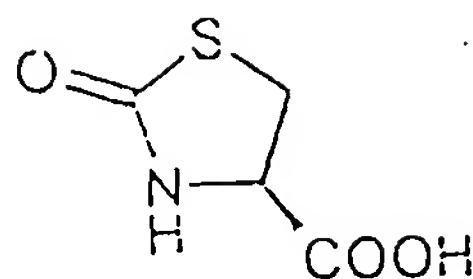
(PII)



(PIII)

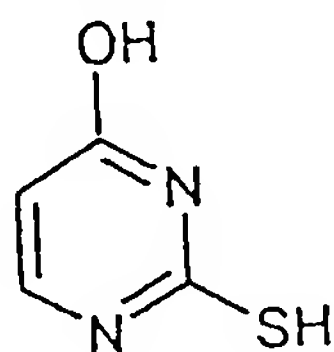


(PIV)



(PV)

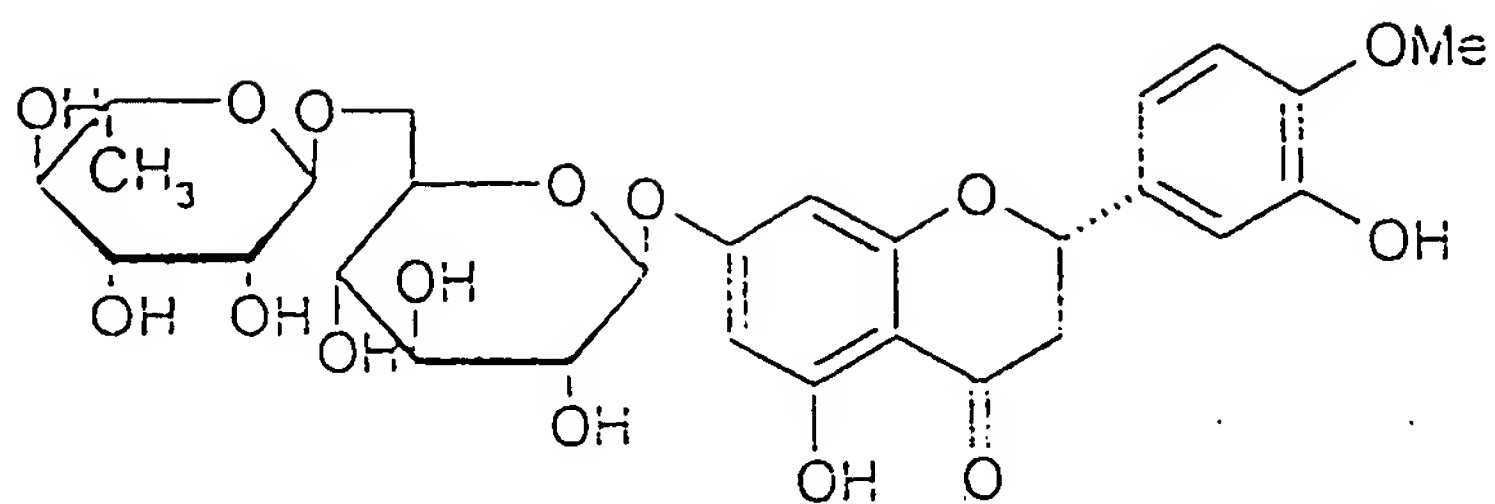
mono and polyalcohols or thiols: 2-thiouracil (QI), 2-mercaptoethanol (QII), esperidine (QIII), secalciferol (QIV), 1- α -OH vitamin D2 (QV), flocalcitriol (QVI), 22-oxacalcitriol (QVII), the vitamin D3 derivative esterified with the vitamin A radical (QVIII), the compound of formula (QIX), 24,28-methylene-1 α -hydroxyvitamin D2 (QX) the compound derived from 1 α ,25-dihydroxyvitamin D2 (QXI), 2-mercaptoimidazol (QXII)



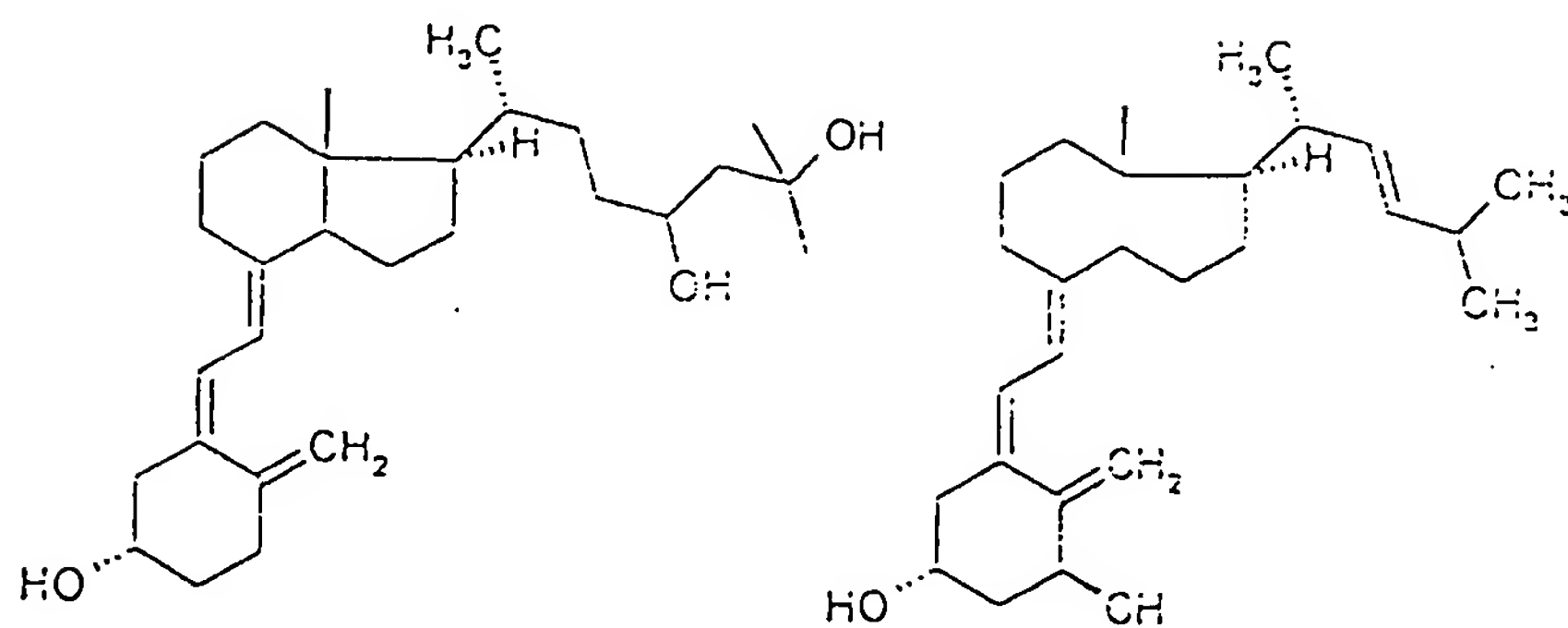
(QI)



(QII)

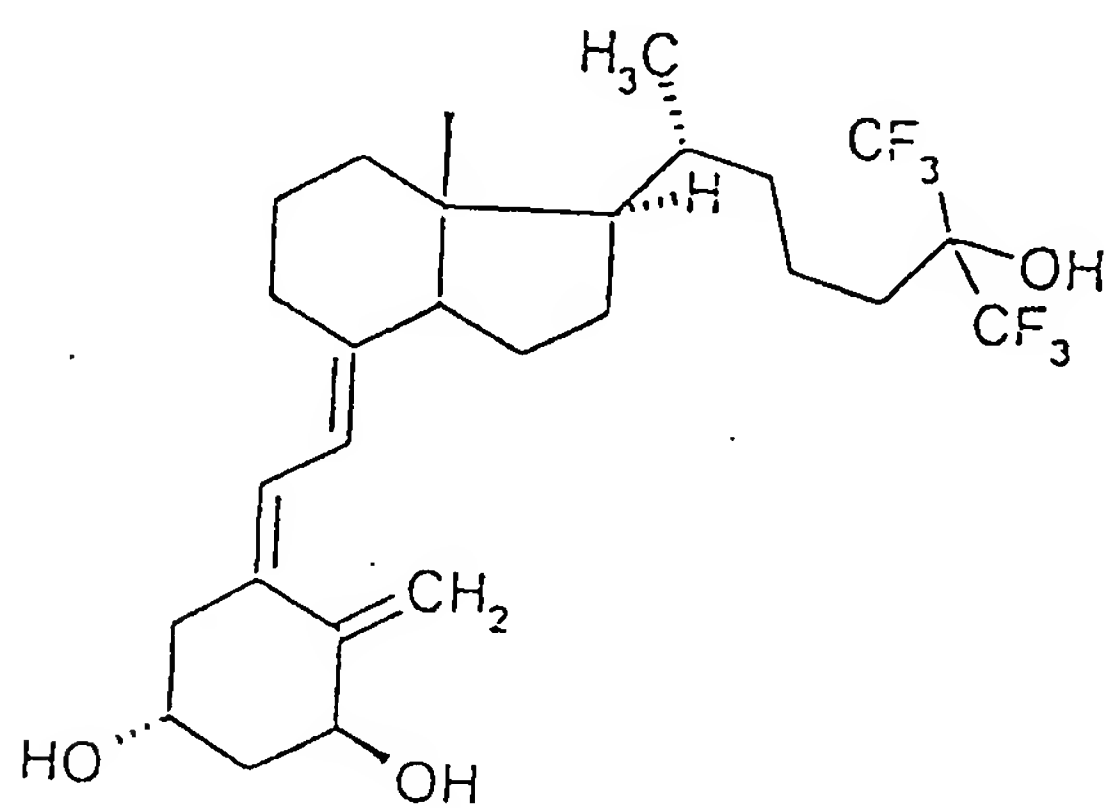


(QIII)

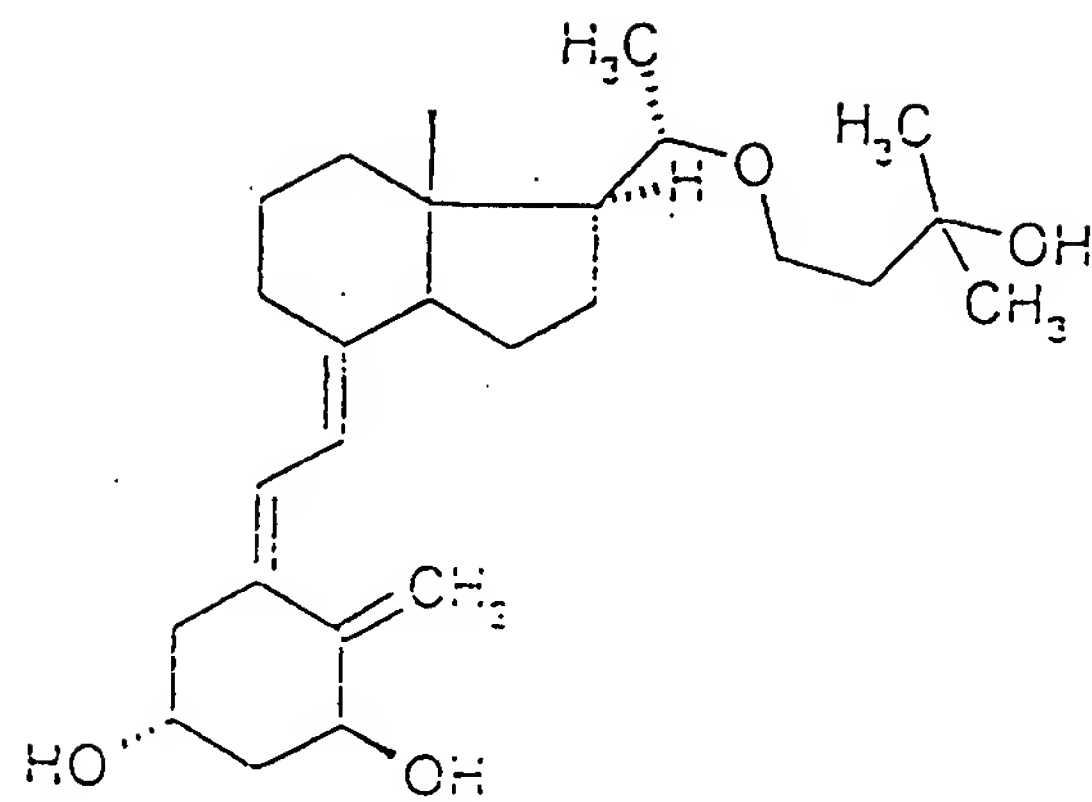


(QIV)

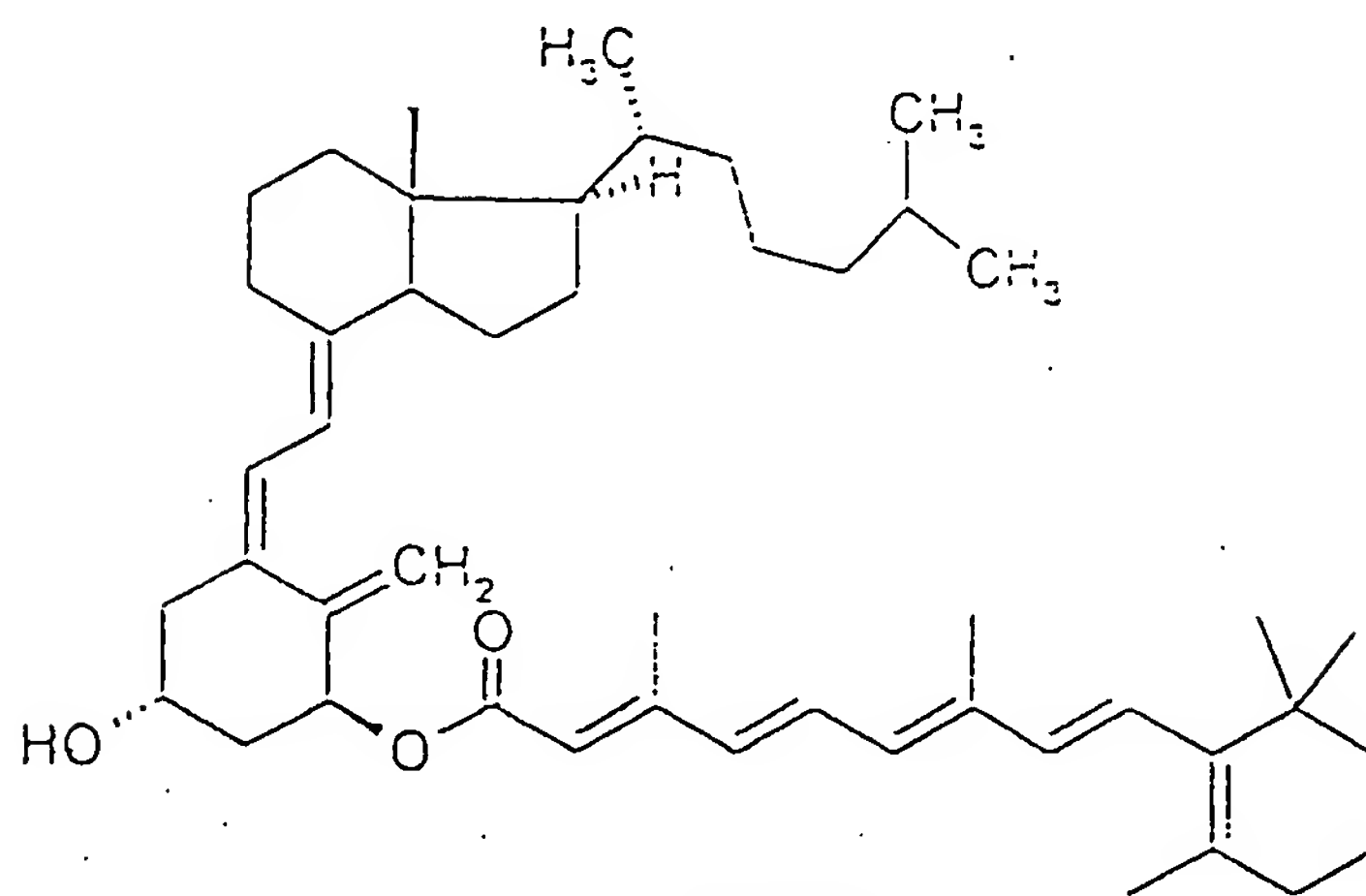
(QV)



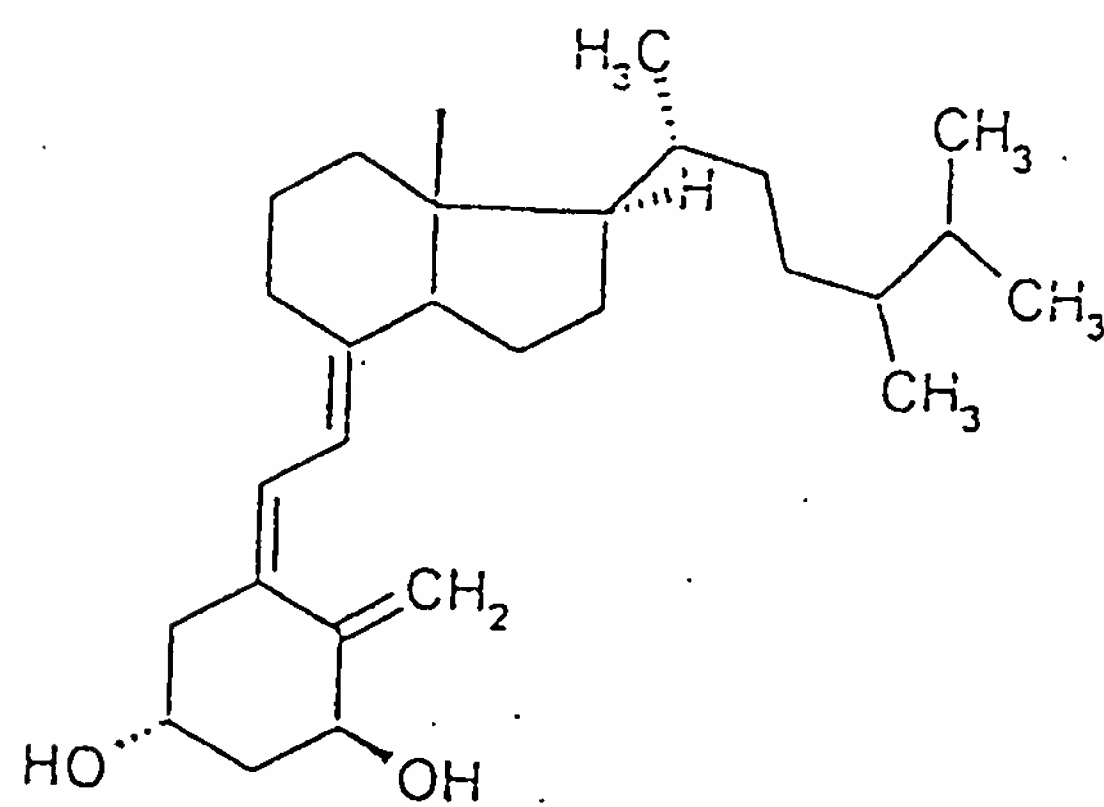
(QVI)



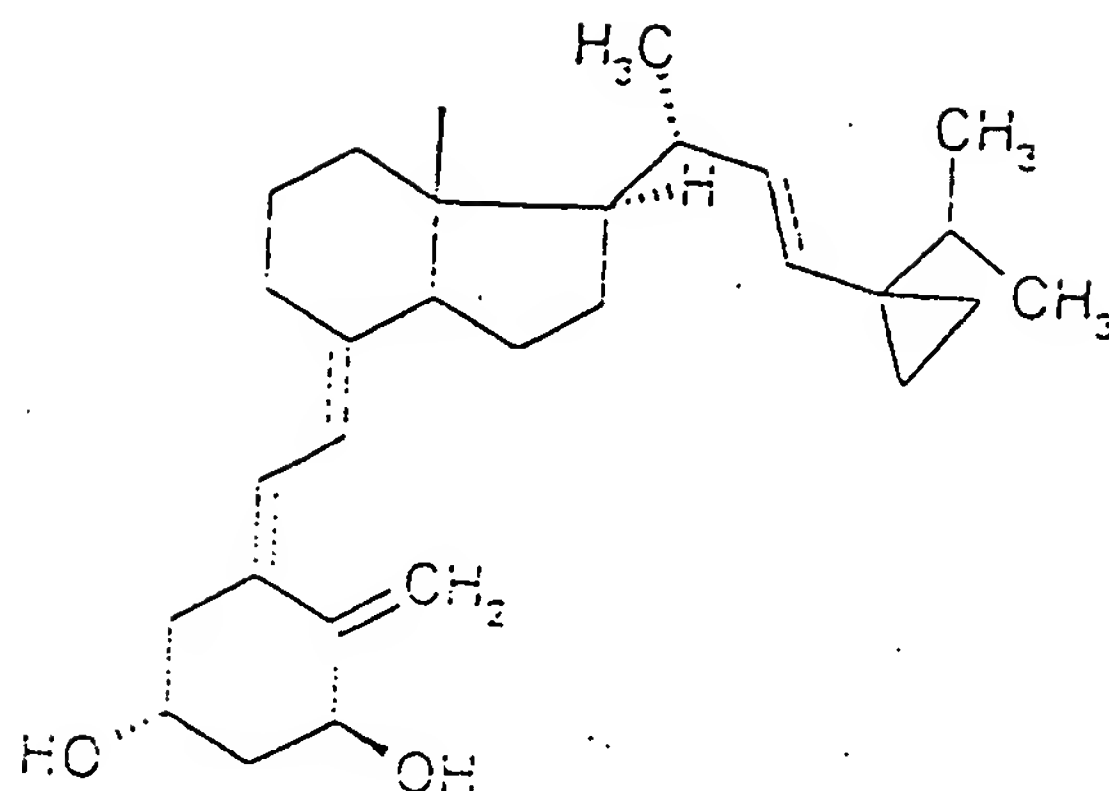
(QVII)



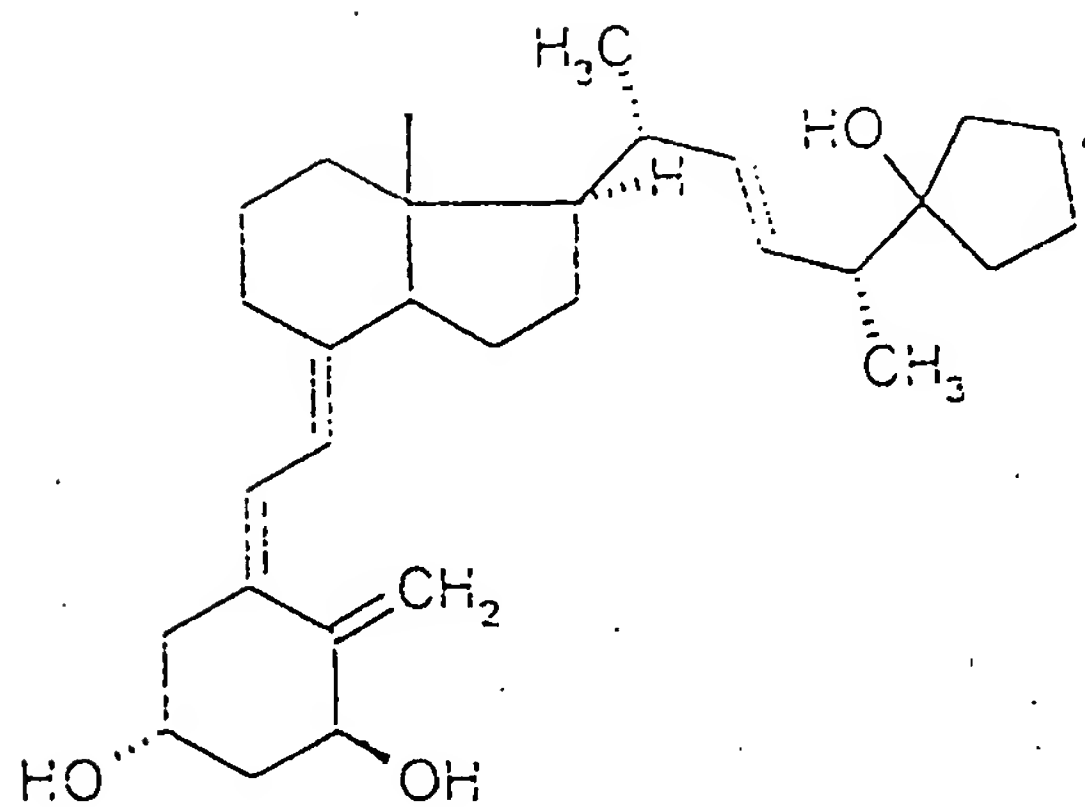
(QVIII)



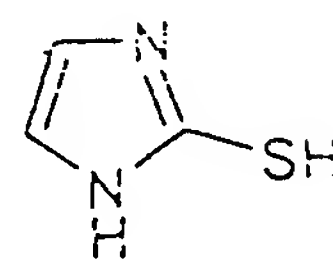
(QIX)



(QX)

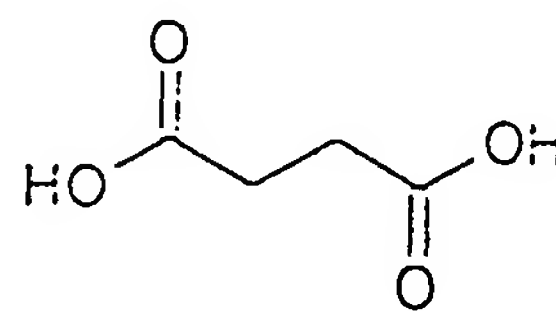


(QXI)



(QXII)

- succinic acid (RI)



(RI)

The drug precursor compounds either of B or B₁, or of C = -T_C-Y-H are prepared according to the known methods in the prior art, and described for example in "The Merck Index, 12a Ed. (1996), herein incorporated by reference. When available, the corresponding isomers and optical isomers can be used.

The derivative of vitamin D3 with retinoic acid (QVIII) is prepared as described in JP 93039261 (ref. C.A. 119 117617); the compound of formula (QIX) according to EP 562,497; 24,28-methylene-1 α -hydroxyvitamin D2 (QX) according to EP 578,494; the derivative compound of dehydroxyvitamin D2 (QXI) according to EP 549,318.

The tests carried out to identify the drug corresponding to the R radical of the formulas (I) and (II) are in detail the following:

Test 1 (NEM): evaluation of the gastrointestinal damage from oxidative stress induced by free radicals formed following administration of N-ethylmaleimide (NEM) (H.G. Utley, F. Bernheim, P. Hochstein "Effects of sulphhydryl reagents on peroxidation in microsomes" Archiv. Biochem. Biophys. 118, 29-32 1967).

The animals (rats) are distributed in the following groups (no. 10 animals for group):

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v

of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, or a physiologic solution when parenterally administered, i.e. by subcutaneous, intraperitoneal, intravenous or intramuscular route),
2° group: treatment: carrier as above defined + NEM,

B) Groups treated with the drug:

group I: treatment: carrier + drug,

gruppo II: treatment: carrier + drug + NEM.

The administration routes are those known for the drug, and can be the oral or subcutaneous, intraperitoneal, intravenous or intramuscular route.

The NEM dose is of 25 mg/kg in physiologic solution (subcutaneous route) and the drug is administered one hour later, in suspension in the carrier, as a single dose which corresponds to the maximum one, or the highest still tolerated by the animals of the group of rats not pretreated with NEM, i.e. the highest administrable dose to said group at which there is no manifest toxicity in the animals, defined as a toxicity that is clearly recognizable for its symptoms. The animals are sacrificed after 24 hours and then one proceeds to the evaluation of the damage to the gastrointestinal mucosa.

The drug meets test 1, i.e. it can be used to prepare the compounds of general formula (I) and (II), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in said group the gastrointestinal damages noticed

are greater than those shown by the group treated with the carrier alone, or the group treated with carrier + drug, or the group treated with carrier + NEM, even though the drug pharmacotherapeutic efficacy, assayed by using specific tests, is not significantly reduced.

Test 2 (CIP): Protection parameter of endothelial cell against the oxidative stress induced by cumene hydroperoxide (CIP).

Human endothelial cells of the umbilical vein are prepared according to an usual standard procedure. Fresh umbilical veins are filled with a 0.1% by weight collagenase solution and incubated at 37°C for 5 minutes.

Afterwards the veins are perfused with medium M 199 (GIBCO, Grand Island, NY) pH 7.4 further added of other substances, as described in the examples. The cells are collected from the perfusate by centrifugation and harvested in culture flasks T-75, pretreated with human fibronectin. The cells are then harvested in the same medium, further added with 10 ng/ml of bovine hypothalamic growth factor. When the cells of the primary cell culture (i.e. that directly obtained from ex-vivo) form a single layer of confluent cells (about 8,000,000 cells/flask), the culture is stopped and the layers washed and trypsinized. The cellular suspensions are transferred into the wells of a cell culture plate having 24 wells, half of which is then additioned with the same culture medium containing the

drug at a 10^{-4} M concentration, and harvested in a thermostat at 37°C at a constant moisture. Only the cells coming from said first sub-cultures are used for the experiments with cumene hydroperoxide (CIP). The cells are identified as endothelial cells by morphological examination and by their specific immunological reaction towards factor VIII; said cultures did not show any contaminations from myocytes or fibroblasts.

Before starting the test, the cellular culture medium is removed and the cellular layers are carefully washed with a physiologic solution at a temperature of 37°C. The wells of the culture plate are then incubated for one hour with CIP at a 5 mM concentration in the culture medium. The evaluation of cellular damage (apoptosis) is carried out by determining the per cent variation of the DNA fragmentation with respect to the control group (treated with CIP alone), evaluating the fluorescence variation at the wave length of 405-450 nm. 5 replicates for each sample are carried out.

The drug meets the test, i.e. it can be used for preparing the compounds of general formula (I) and (II), when a statistically significant inhibition of apoptosis (cellular damage) induced by CIP with respect to the group treated with CIP alone is not obtained at $p < 0.01$.

Test 3 (L-NAME): evaluation of the endothelial dysfunction induced by administration of L-NAME (N^W -nitro-L-arginine-methyl ester) J. Clin. Investigation 90, 278-281, 1992.

The endothelial dysfunction is evaluated by determining the damage to the gastrointestinal mucosa, the hepatic damage and blood hypertension induced by administration of L-NAME.

The animals (rats) are divided in groups as herein below shown. The group receiving L-NAME is treated for 4 weeks with said compound dissolved at a concentration of 400 mg/litre in drinking water. The following groups are constituted (No. 10 animals for group):

A) Control groups:

1° group: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, physiologic solution when administered parenterally),

2° group: carrier + L-NAME,

B) Groups administered with the drug:

3° group: carrier + drug,

4° group: carrier + drug + L-NAME.

The administration routes are those known for the drug, and can be the oral or subcutaneous, intraperitoneal, intravenous or intramuscular route. The drug is administered at that dose which results the highest still tolerated by the animals of the group of rats not pretreated with L-NAME, i.e. the highest administrable dose at which there is no evident toxicity in the animals, i.e. a toxicity recognizable for its symptoms. The drug is administered once a

day for 4 weeks.

At the end of the four weeks treatment access to water is prevented and after 24 hours the animals are sacrificed.

One hour before the sacrifice blood-pressure is determined, and a blood pressure increase is taken as an evaluation of the damage to vascular endothelium. The damage to the gastric mucosa is evaluated as illustrated in test 1 (see example F1). The hepatic damage is determined by evaluation of the glutamic-pyruvic transaminase (GPT increase) after sacrifice.

The drug meets test 3, i.e. it can be used for preparing the compounds of general formula (I) and (II), when in the group of rats treated with L-NAME + drug + carrier it is found an higher hepatic damage (GPT) and/or an higher gastric damage and/or an higher cardiovascular (blood-pressure) damage in comparison to that of the group treated with the carrier alone, or of the group treated with carrier + drug, or of the group treated with carrier + L-NAME; even if the drug pharmacotherapeutic efficacy, assayed by specific tests, is not significantly reduced.

Under the conditions indicated in the above described in vivo tests 1 and 3 the therapeutic index of the drug is reduced since the usual doses at which the drug can be effective are no longer tolerated.

It has been found by the Applicant that the precursors of

B or B₁ do not meet test 4 reported hereinafter while they meet, as said, test 5.

Test 4 is a colorimetric test which must not be satisfied by the precursor of B or B₁ (precursor of the X₂ or X_{2a} of the formulas (I) and (II) respectively). The inhibition of the production of radicals from DPPH (2,2-diphenyl-1-picryl-hydrazyl) is described in M.S. Nenseter et Al., Atheroscler. Thromb. 15, 1338-1344, 1995. 100 µM solutions in methanol of the tested substances are prepared, and an aliquot of each of said solutions is added to a DPPH solution in methanol 0.1 M. After having stored the solutions at room temperature away from light for 30 minutes, their absorbances are read at the wavelength of 517 nm, together with that of the corresponding DPPH solution at the same concentration. The absorbance decrease with respect to that of the solution of DPPH at the same concentration of the test solutions is determined. The effectiveness of the tested compound in inhibiting formation of radicals by DPPH is expressed by the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the test compound together with DPPH and of the solution containing only DPPH. Test 4 is satisfied when the inhibition is equal or greater than 50%.

Test 5 is a colorimetric test wherein 0.1 ml aliquots of 10⁻⁴ M methanolic solutions of the tested products are added to

test tubes containing a solution formed by 0.2 ml of 2 mM desoxyribose, 0.4 ml of phosphate buffer pH 7.4 100 mM and 0.1 ml of 1 mM $\text{Fe}^{II}(\text{NH}_4)_2(\text{SO}_4)_2$ in 2mM HCl. The test tubes are then maintained at 37°C for one hour. Then in each test tube 0.5 ml of a 2.8% solution in water of trichloroacetic acid and 0.5 ml of an aqueous 0.1 M solution of thiobarbituric acid are added, in the order. A reference blank is formed by adding to a test tube containing only the above described aqueous solution of reactants 0.1 ml of methanol. The test tubes are closed and heated in an oil bath at 100°C for 15 minutes. A pink coloration is developed the intensity of which is proportional to the quantity of desoxyribose undergone to radical oxidative degradation. The solutions are cooled at room temperature and their absorbances are read at 532 nm against the blank. The inhibition induced by the precursor of B or B₁ or C = -T_c-Y-H in the confront of radical production by Fe^{II} is determined by means of the following formula:

$$(1 - A_b/A_c) \times 100$$

wherein A_b and A_c are respectively the absorbance values of the solution containing the tested compound + the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage of radical production as above defined from the precursor of B or B₁ or C = -T_c-Y-H is higher than or equal to 50%.

Unexpectedly the invention products of the formulas (I)

and (II) have an improved therapeutic index, in oxidative stress conditions, compared with the precursor drugs.

For illustrative purposes the above mentioned tests are referred to the following compounds (see the Examples):

Test 1: precursor drug: indomethacin

- Maximum administrable dose to rats: 7.5 mg/Kg p.o. By administering a higher dose a toxicity is manifested, characterized by enteropathy, tremor, sedation until death (within 24 hours).
- The group of rats treated with NEM + indomethacin at the above mentioned dose shows gastrointestinal damages.

Since indomethacin in the groups treated with NEM causes gastrointestinal damages, it meets test 1. Indomethacin can therefore be used as a drug for preparing the compounds (I) and (II) of the present invention.

Test 2: precursor drugs: indomethacin, paracetamol and mesalamine

Indomethacin and paracetamol meet test 2 since the cellular damage (apoptosis) inhibition induced by CIP is not significantly different with respect to that of the controls.

Therefore the above drugs can be used as drugs for preparing the compounds (I) and (II) of the present invention.

On the contrary mesalamine does not meet test 2, since it inhibits the apoptosis induced by CIP. Therefore mesalamine

according to test 2 could not be used as a precursor to prepare the compounds (I) and (II) of the present invention. It has been however found that mesalamine submitted to test 1 causes gastrointestinal damages.

Thus also mesalamine can be used as a precursor for preparing the compounds (I) and (II) of the present invention. Test 3 (L-NAME) precursors drugs: paracetamol, simvastatin, omeprazole

Paracetamol and simvastatin meet test 3 since they cause gastric and hepatic damages greater than those induced both by L-NAME + carrier and by the drug + carrier.

Therefore they can be used as precursors to prepare the compounds (I) and (II) of the present invention.

On the contrary it has been found that omeprazole neither causes gastric nor hepatic damages, nor influences blood-pressure. According to test 3 omeprazole could not be used as a precursor for preparing the compounds (I) and (II) of the present invention.

Test 4 (test for the precursor of B and B₁): precursor compound: N-acetylcysteine and 4-thiazolidincarboxylic acid

N-acetylcysteine in said test inhibits of 100% the production of radicals induced by DPPH. Since said percentage is higher than the limit of 50%, said drug cannot be used in the present invention as precursor of B or B₁.

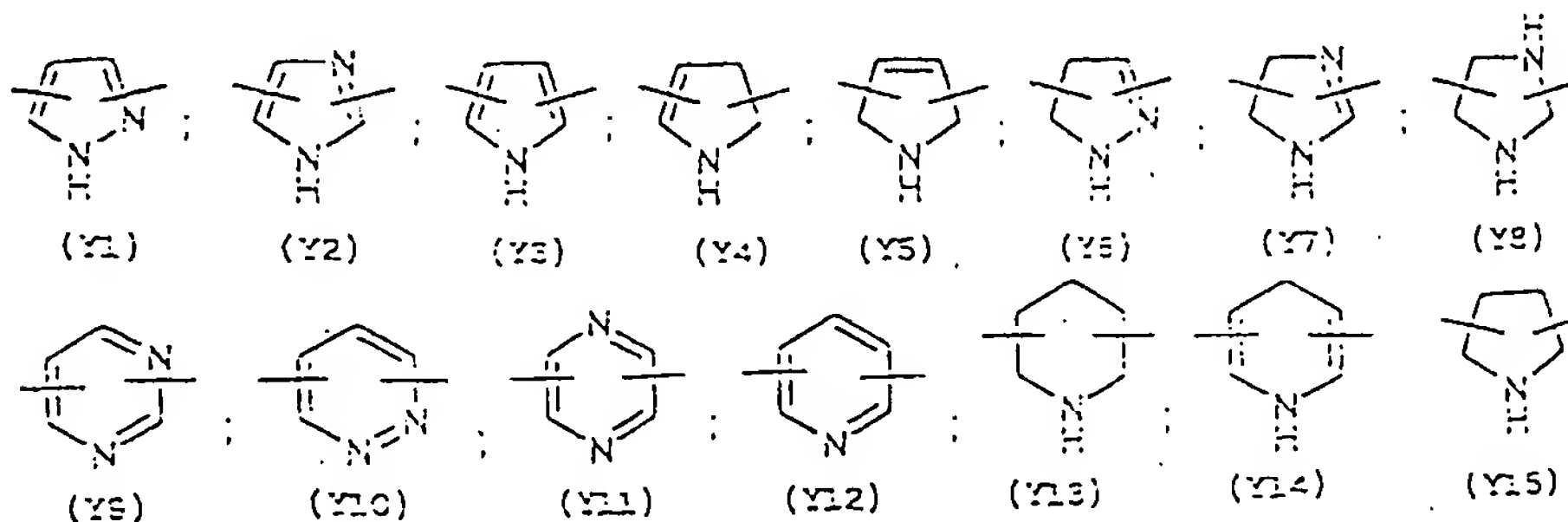
4-Thiazolidincarboxylic acid does not inhibit at any

extent the production of radicals induced by DPPH (Table V). Thus the drug does not meet test 4 as requested by the instant invention and it could be used as a precursor of B or B₁ if it meets test 5.

Test 5 (test for the precursor of B, B₁ and C= -T_C-Y-H):
precursor compound: 4-thiazolidincarboxylic acid

Table III relating to this test shows that the 4-thiazolidincarboxylic acid meets test 5 since the % inhibition is of 100%. Therefore the compound can be used as precursor of B or of B₁.

Y³ in formula (III) is preferably selected from the following:



The most preferred of Y³ is Y12 (pyridyl) substituted in positions 2 and 6. The bonds can also be in asymmetric position, for example Y12 (pyridyl) can be substituted also in position 2 and 3; Y1 (pyrazol) may be 3,5-disubstituted.

The compounds according to the present invention of formula (I) and (II) can be transformed into the corresponding

salts. For example one way to form salts is the following: when in the molecule one nitrogen atom sufficiently basic to be salified, by reaction in organic solvent such as for example acetonitrile, tetrahydrofuran, is present, it is reacted with an equimolecular amount of the corresponding organic or inorganic acid. To form the salt, preferably in the formula of the invention compound Y or Y' of formula (III) is present.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acids.

Examples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acids.

The derivatives according to the invention can be used in the therapeutic indications of the precursor drug, allowing to obtain the advantages exemplified hereinafter for some groups of these drugs:

- Anti-inflammatory drugs NSAIDs: the invention compounds result very well tolerated and effective, even when the organism is debilitated and is under conditions of oxidative stress. Said drugs can be used also in those pathologies wherein inflammation plays a significant pathogenetic role, such as for instance, but not limited to, in cancer, asthma, miocardic infarction.
- Adrenergic blockers, of α - or β -blocker type: the action spectrum of the compounds of formula (I) results wider than that of the starting drugs: to a direct action on the

smooth musculature the inhibition of the nervous beta-adrenergic signals governing the contraction of the hematic vessels is associated. The side effects (dyspnoea, bronchoconstriction) affecting the respiratory apparatus are lower.

- Antithrombotic drugs: the antiplatelet activity is potentiated and in the case of the aspirin derivatives the gastric tolerability is improved.
- Bronchodilators and drugs active on the cholinergic system: the side effects affecting the cardio-vascular apparatus (tachycardia, hypertension) result lowered.
- Expectorants and mucolytic drugs: the gastrointestinal tolerability results improved.
- Diphosphonates: the toxicity relating to the gastrointestinal tract is drastically lowered.
- Phosphodiesterase (PDE) inhibitors (bronchodilators): the therapeutic efficacy is improved, the dosage being equal; it is therefore possible, using the compounds of the invention to administer a lower dose of the drug and reduce the side effects.
- Anti leukotrienic drugs: better efficacy.
- ACE inhibitors: better therapeutic efficacy and lower side effects (dyspnoea, cough) affecting the respiratory apparatus.
- Antidiabetic drugs (insulin-sensitizing and

hypoglycaemizing), antibiotic, antiviral, antitumoral, anticolitic drugs, drugs for the dementia therapy: better efficacy and/or tolerability.

The drugs which can be used as precursors in the general formula of the compounds of the invention are all those meeting at least one of the above mentioned tests 1, 2, 3. Examples of precursor drugs which can be used are the following:

For anti-inflammatory/analgesic drugs, the following can for example be mentioned:

anti-inflammatory drugs: aceclofenac, acemetacin, acetylsalicylic acid, 5-amino-acetylsalicylic acid, alclofenac, alminoprofen, amfenac, bendazac, bermoprofen, α -bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen, cinmetacin, clidanac, clopirac, diclofenac sodium, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, oxaceprol, oxaprozin, oxyphenbutazone, parsalmide, perisoxal, phenyl acetylsalicylate, olsalazine, pyrazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicilamide O-

acetic acid, salicylsulphuric acid, salsalate, sulindac, suprofen, suxibuzone, tenoxicam, tiaprofenic acid, tiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepirac, tomoxiprol;

analgesic drugs: acetaminophen, acetaminosalol, aminochlorthenoxazin, acetylsalicylic 2-amino-4-picoline acid, acetylsalicylsalicylic acid, anileridine, benoxaprofen benzylmorphine, 5-bromosalicylic acetate acid, bucetin, buprenorphine, butorphanol, capsaicine, cinchophen, ciramadol, clometacin, clonixin, codeine, desomorphine, dezocine, dihydrocodeine, dihydromorphine, dimepheptanol, dipyroceryl, eptazocine, ethoxazene, ethylmorphine, eugenol, floctafenine, fosfosal, glafenine, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, p-lactophenetide, levorphanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nicomorphine, norlevorphanol, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, phenocoll, phenoperidine, phenylbutazone, phenylsalicylate, phenylramidol, salicin, salicylamide, tiorphan, tramadol, diacerein, actarit.

For respiratory and urogenital apparatus drugs (bronchodilators and drugs active on the cholinergic system, expectorants/mucolytics, antiasthmatic/antiallergic antihistaminic drugs), the following can be mentioned:

broncodilators and drugs active on the cholinergic system:

acefylline, albuterol, bambuterol, bamifylline, bevonium methyl

sulphate, bitolterol, carbuterol, clenbuterol, chlorprenaline, dioxethedrine, difylline, ephedrine, epinephrine, eprozinol, etafredine, ethylnorepinephrine, etofylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium bromide, isoetharine, isoprotenerol, mabuterol, metaproterenol, oxybutynin, oxitropium bromide, pirbuterol, procaterol, protokylol, proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, 1-teobromineacetic acid, tiotropium bromide, tretoquinol, tulobuterol, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetra hydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: ambroxol, bromhexine, domidol, erdosteine, guaiacol, guaifenesin, iodinated glycerol, letosteine, mesna, sobrerol, stepronin, terpin, tiopronin;

antiasthmatic/antiallergic antihistaminic drugs: acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam, chromoglycate, chromolyn, epinastine, fexofenadine, formoterol, histamine, hydroxyzine, levocabastine, lodoxamide, mabuterol, metron s, montelukast, nedocromil, repirinast, seratrodist, suplatast tosylate, terfenadine, tiaramide, urushiol, bromhexine.

For cardiovascular drugs (ACE-inhibitors, beta-blockers, antithrombotic and vasodilator drugs, antidiabetic and hypoglycemic drugs), the following can be mentioned:

ACE-inhibitors: alacepril, benazepril, captopril, cero-

napril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, losartan, moveltipril, naphthopidil, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, urapidil;

beta-blockers: acebutolol, alprenolol, amosulalol, arotinolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, dilevalol, epanolol, esmolol, indenolol, labetalol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipridalol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol;

antithrombotics and vasodilators: acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betahistine, brovincamine, bufeniode, citicoline, clobenfurool, clopidogrel, cyclandelate, dalteparin, dipyridamol, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, heparin, lamifiban, midrodine, nadroparin, nicotinoyl alcohol, nylidrin, ozagrel, perhexiline, phenylpropanolamine, prenylamine, papaveroline, reviparin sodium salt, ridogrel, suloctidil, tinofedrine, tinzaparin, triflusal, xanthinol niacinate;

antidiabetic drugs : acarbose, carbutamide, glibornuride glybuthiazol(e), miglitol, repaglinide, troglitazone, 1-butyl-

3-metanyl-urea, tolrestat, nicotinamide.

For antitumoral drugs, the following can be mentioned: ancitabine, anthramycin, azacitidine, azaserine, 6-azauridine, bicalutamide, carubicin, carzinophilin, chlorambucil, chlorozotocin, cytarabine, daunorubicin, defosfamide, demecolcine, denopterin, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicin, droloxifene, edatrexate, eflornithine, enocitabine, epirubicin, epitiostanol, etanidazole, etoposide, fenretinide, fludarabine, fluorouracil, gemcitabine, hexestrol, idarubicin, lonicamine, mannomustine, melphalan, menogaril, 6-mercaptopurine, methotrexate, mitobronitol, mitolactol, mitomycins, mitoxantrone, mopidamol, mycophenolic acid, ninopterin, nogalamycin, paclitaxel, pentostatin, pirarubicin, piritrexim, plicamycin, podophyllic acid, porfimer sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, thiamiprine, thioguanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicin.

For antiulcer drugs the following can be mentioned: ϵ -acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecbet, enprostil, esaprazole, irsogladine, misoprostol, omeprazole, ornoprostil, pantoprazole, plaunotol, rioprostil, rosaprostol, rotraxate, sofalcone, trimoprostil.

Among anti-hyperlipidemic drugs (statines) the following

can be mentioned: atorvastatin, cilastatin, dermostatin, fluvastatin, lovastatin, mevastatin, nystatin, pentostatin, pepstatin, privastatin sodium, simvastatin.

Among antibiotic/antiviral drugs the following can be mentioned:

antibiotics: amdinocillin, amoxicillin, ampicillin, apalcillin, apicycline, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoylpas, benzyl penicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephradine sodium, cephalalexin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cephapirin sodium, cephradine, chloramphenicol, chlortetracycline, cinoxacin, clavulanic acid, clometocillin, cloxacillin, cyclacillin, cycloserine, demeclocycline, dicloxacillin, epicillin, fenbecillin, flomoxef, floxacillin, etacillin, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, meclocycline, meropenem, metampicillin, methacycline, methicillin sodium, mezlo-

cillin, minocycline, moxalactam, mupirocin, myxin, negamycin, novobiocin, oxacillin, panipenem, penicillin G potassium salt, penicillin N, penicillin O, penicillin V, phenethicillin potassium salt, pipacycline, piperacillin, pirlimycin, porfirimycin, propicillin, quinacillin, ritipenem, rolitetracycline, sancycline, sedecamycin, spectinomycin, sulbactam, sulbenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidin, azithromycin, clarithromycin, dirthromycin, enviomycin, erythromycin, josamycin, midecamycin, miokamycin, oleandomycin, rifabutin, rifamide, rifamycin, rifaximin, rokitamycin, spiramycin, troleandomycin, viomycin, virginiamycin;

amikacin, apramycin, arbekacin, dibekacin, dihydrostreptomycin, fortimicins, gentamicin, micronomicin, neomycin, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin;

bacampicillin, cefcapene pivoxil, cefpodoxime proxetil, panipenem, pivampicillin, pivcefalexin, sultamicillin, talampicillin;

carbomycin, clindamycin, lincomycin, mikamycin, rosaramicin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, flumequine, grepafloxacin, lomefloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rufloxacin, sparfloxacin, tosufloxacin, trovafloxacin,

clomocycline, guamecycline, oxytetracycline, nifurpirinol, nifurprazine; p-aminosalicylic acid, p-aminosalicylic acid hydrazide, clofazimine, deoxydihydrostreptomycin, ethambutol, glyconiazide, isoniazid, opiniazide, phenyl aminosalicylate, rifampin, rifapentine, salinazid, 4-4'-sulfynyldianiline, Acediasulfone, dapsona, succisulfone, p-sulfanilylbenzylamine, thiazolsulfone, acetyl sulfamethoxypyrazine, mafenide, 4'-(methylsulfamoyl)sulfanilanilide, salazosulfadimidine, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 2-p-sulfanilylanilinoethanol, N⁴-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfisomidine, sulfisoxazole, 4-sulfanilamido salicylic acid; negamycin, carumonan, cloxyquin, nitroxoline, arginine, metronidazole;

antiviral drugs: acyclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, indanavir, kethoxal,

lamivudine, MADU, penciclovir, podophyllotoxin, ribavirin, rimantadine, saquinavir, sorivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine.

Among bone resorption inhibitors (diphosphonates) the following can be mentioned: alendronic acid, butedronic acid, etidronic acid, oxidronic acid, pamidronic acid, risedronic acid.

Among antidemence drugs the following can be mentioned: amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

The preferred substances are the following:

among anti-inflammatory drugs: acetylsalicylic acid, 5-aminoacetylsalicylic acid, carprofen, diclofenac sodium, diflunisal, etodolac, flufenamic acid, flunixin, flurbiprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, naproxen, niflumic acid, olsalazine, piroxicam, salsalate, sulindac, suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, tolmetin, zomepirac, tomoxiprol;

among analgesic drugs: acetaminophen, acetylsalicylsalicylic acid, benoxaprofen, buprenorphine, butorphanol, capsaicin, diacerein, dihydrocodeine, ethylmorphine, eugenol, phenylbutazone, meptazinol, morphine, nalbuphine, pentazocine, thiorphan,

tramadol, actarit.

Among respiratory and urogenital apparatus drugs:
(bronchodilators, drugs active on the cholinergic system,
expectorants/mucolytics, antiasthmatics/antiallergic antihista-
minic drugs):

bronchodilators and drugs active on the cholinergic
system: albuterol, carbuterol, clenbuterol, difylline,
etofylline, fenoterol, ipratropium bromide, metaproterenol,
oxybutynin, pirbuterol, salmeterol, terbutaline, tiotropium
bromide, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-
N-(1,2,3,6-tetrahydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: ambroxol, bromexine, guaia-
col, sobrerol;

antiasthmatic/antiallergic antihistaminic drugs:
cetirizine, chromoglycate, histamine, levocabastine,
lodoxamide, montelukast, terfenadine, bromexine.

Among cardiovascular drugs:

ACE-inhibitors: captopril, enalapril, lisinopril, losar-
tan, ramipril;

beta blockers: alprenolol, atenolol, bupranolol,
labetalol, metipranolol, metoprolol, pindolol, propranolol, ti-
molol;

antithrombotic and vasoactive drugs: acetylsalicylic acid,
acectorphan, argatroban, clopidogrel, dalteparin, dipyridamole,
enoxaparin, heparin, iloprost, midodrine, ozagrel,

phenylpropanolamine, trifusal;

antidiabetic drugs: tolrestat, nicotinamide.

Among antitumoral drugs: anthramycin, daunorubicin, doxorubicin, epirubicin, fluorouracil, methotrexate, vinblastine.

Among antiulcer drugs: cimetidine, omeprazole, pantoprazole.

Among antihyperlipidemic drugs: lovastatin, pravastatin sodium, simvastatin.

Among antibiotic/antiviral drugs:

antibiotic drugs: amoxicillin, ampicillin, aztreonam, biapenem, carbenecillin, cefaclor, cefadroxil, cefamandole, cefatrizine, cefoxitin, clavulanic acid, dicloxacillin, imipenem, meclocycline, methacycline, moxalactam, panipenem, sulbactam, azithromycin, erythromycin, josamycin, miokamycin, rifabutine, rifamide, rifamycin, gentamicin, paromomycin, sisomicin, bacampicillin, carbomycin, clindamycin, ciprofloxacin, clinafloxacin, difloxacin, enrofloxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pipemidic acid, apicycline, clomocycline, oxytetracycline, nifurpirinol, nifurprazine, isoniazid, rifampin, rifapentine, dapsone, thiazolsulfone, sulfamethoxazole, sulfamoxole, metronidazole, arginine;

antiviral drugs: acyclovir, famciclovir, ganciclovir, penciclovir, ribavirin, vidarabine, zidovudine.

Among bone resorption inhibitors: alendronic acid, etidronic acid, pamidronic acid.

Among antidementia drugs: oxiracetam, tacrine, velnacrine.

The above mentioned substances, A precursors, are prepared according to the methods known in the prior art. See for example in "The Merck Index, 12a Ed. (1996), herein incorporated by reference. When available, the corresponding isomers, comprising optical isomers, can be used.

Tomoxiprol is obtained according to the method described in EP 12,866.

The compounds of formula (I) or (II) are prepared with synthesis methods mentioned below.

The choice of the reactions for each method depends on the reactive groups present in the precursor drug molecule, in the precursor compound of B or B₁, which can be, as above mentioned, bivalent or monovalent, and in the precursor compound of C.

The reactions are carried out with methods well known in the prior art, which allow to obtain bonds among the precursor drug, the precursor drug of B or B₁ and the precursor compound of C as above defined.

When the reactive function of the precursor drug (for example -COOH, -OH) is engaged in a covalent bond, for example of ester, amide, ether type, said function can be restored with the methods well known in the prior art.

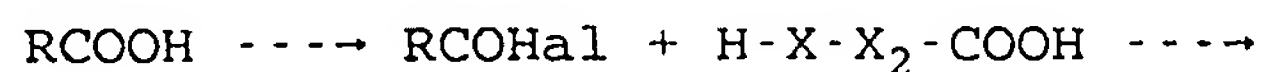
Some synthesis schemes for obtaining the compounds of the invention are reported hereinafter:

A) Synthesis of the compounds of formula (I).

1. Synthesis of the compound obtained by reaction between the precursor drug and the compound precursor of B.

1a. When the drug has general formula R-COOH and the functional group of the precursor compound of B which binds itself to the drug carboxylic function has the formula XZ, X being as above defined and Z = H, the reactions carried out depend on the nature of the second reactive group present in the precursor compound of B.

1a.1 When the second reactive group present in the precursor compound of B is a carboxylic group, the synthesis general scheme expects the initial formation of the halide of the R-COHal acid (Hal = Cl, Br) and the subsequent reaction with the HX group of the precursor compound of B:



X₂, T₁, T_B being as above defined.

When in the two reaction compounds other functional groups COOH and/or HX are present, they must be protected before the reaction according to the methods known in the art; for example as described in the volume by Th. W. Greene: "Protective groups in organic synthesis", Harvard University Press, 1980.

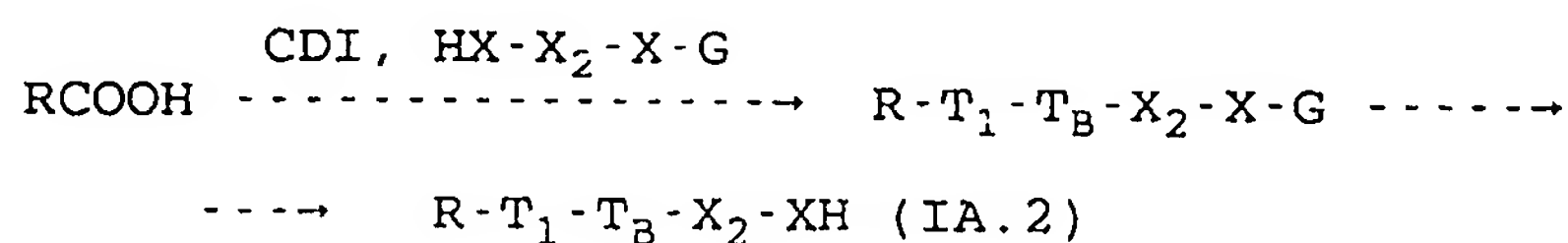
The RCOHal acylhalide is prepared according to the methods known in the prior art, for example by thionyl or oxalyl chloride, P^{III} or P^V halides in inert solvents under the reaction conditions, such as for example toluene, chloroform, DMF, etc.

Specifically, if the HX group of the precursor compound of B is NH_2 , or OH or SH, the precursor drug of formula R-COOH is first converted into the corresponding acyl halide RCOHal, as above mentioned, and then reacted with the HX group of the precursor compound of B in the presence of an organic base, such as triethylamine, pyridine, etc. using an inert solvent in the reaction conditions such as toluene, tetrahydrofuran, etc. at a temperature in the range $0^{\circ}C$ - $25^{\circ}C$.

Alternatively to the previous synthesis, the precursor drug of formula R-COOH can be treated with an agent activating the carboxyl group selected from N,N'-carbonyldiimidazol (CDI), N-hydroxybenzotriazol and dicyclohexylcarbodiimide in solvent such as for example DMF, THF, chloroform etc. at a temperature in the range $-5^{\circ}C$ - $50^{\circ}C$ and the obtained compound let react in situ with the reactive function of the precursor compound of B for obtaining the compound of formula (IA.1).

1a.2 When the precursor compound of B contains two functional groups XZ, equal to or different from each other, X being

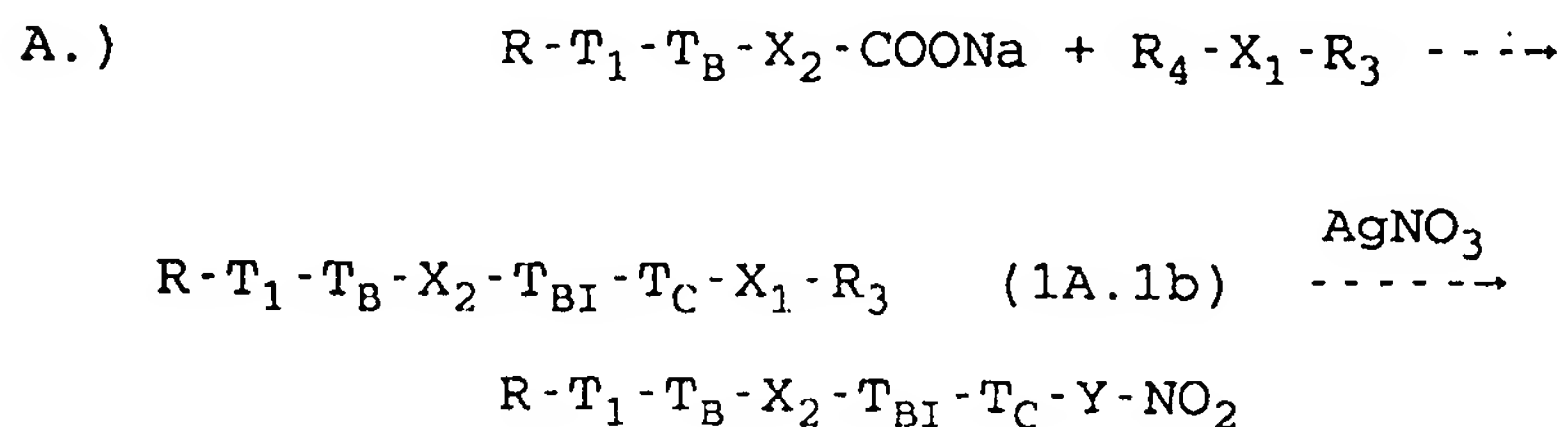
as above defined and $Z = H$, the precursor drug having formula $R-COOH$ is first treated with an agent activating the carboxyl group, as above described in 1a.1, and then with the precursor compound of B, after having protected one of the two reactive HX groups, for example by reaction with acetyl or ter-butyloxycarbonyl, restoring the initial function at the synthesis end. The scheme is the following:



wherein X , T_1 , T_B , X_2 are as above defined and G is a protective group of the HX function.

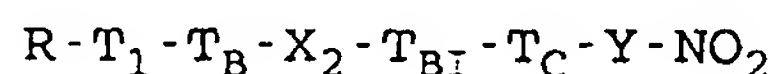
2. Nitroxyderivative synthesis.

2a.1 When the compound obtained at the end of the previous step 1a. has formula (IA.1), the acid can be converted into the corresponding sodic salt and then one can follow the known prior art methods for preparing the final compound, for example according to one of the following synthesis schemes:

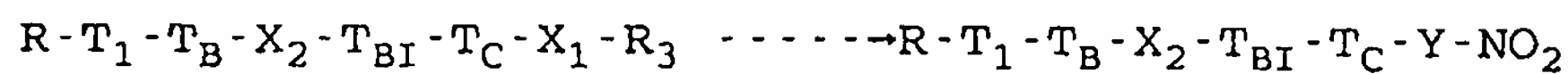
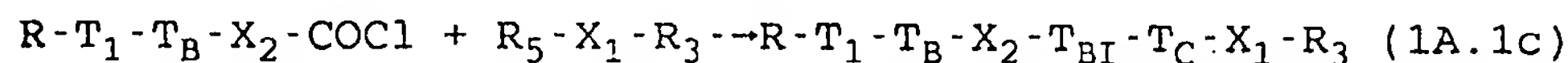


wherein T_1 , T_B , X_2 , T_{BI} , T_C are as above defined, R_4 is selected from Cl , Br , Y is as above defined, X_1 is the Y

radical free from the oxygen atom, R_3 is Cl, Br, Iodine, OH. When $R_3 = OH$ the compound of formula (1A.1b) is submitted to halogenation, for example with PBr_3 , PCl_5 , $SOCl_2$, $PPh_3 + I_2$, and then reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran. If R_3 is Cl, Br, Iodine, the compound of formula (1A.1b) is directly reacted with $AgNO_3$ as above mentioned.



C.)



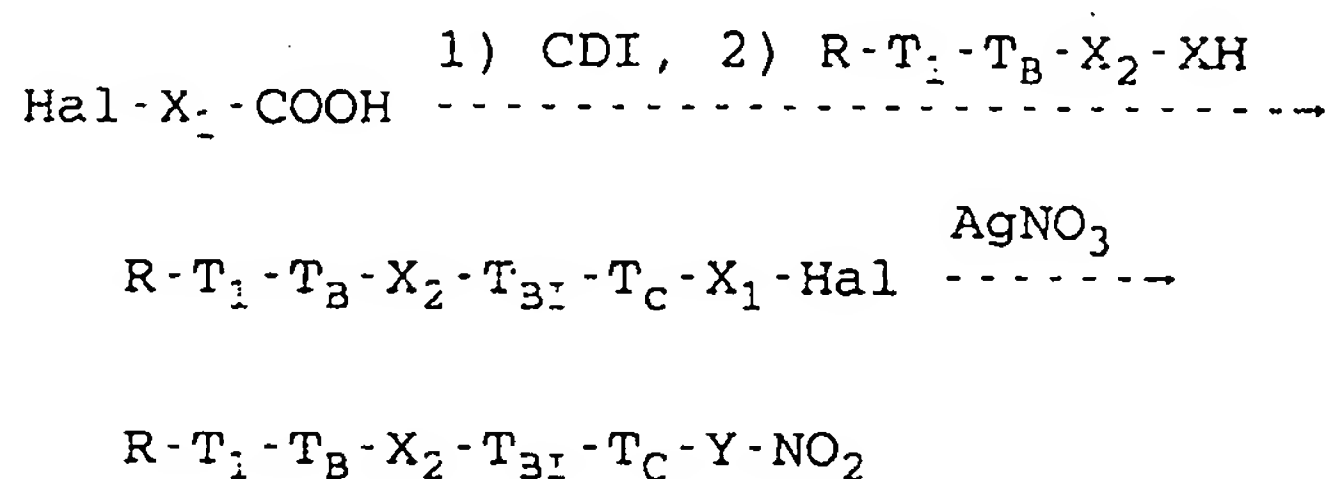
wherein $R_5 = OH$ or NHR_{1C} , R_{1C} , R_3 and the other symbols being as above defined.

The above shown reactions are well known in the prior art. See for example the patent applications in the name of the Applicant WO 94/12463, WO 95/09831 and WO 95/30641.

When X_1 is a linear C_4 alkyl, the corresponding acid $R-T_1-T_B-X_2-COOH$ is reacted with triphenylphosphine in the presence of an halogenating agent such as CBr_4 or N-bromosuccinimide in tetrahydrofuran obtaining the compound (1A.1c) wherein $R_3 = Br$.

2a.2 When the compound obtained at the end of the previous step 1a has formula (IA.2), the corresponding nitroxyderivative

is obtained by treating an halogen-carboxylic acid of formula $\text{Hal-X}_1\text{-COOH}$, X_1 being as above defined, first with an agent activating the carboxyl group as described in 1A.1, and then with the compound of formula (IA.2), obtaining an halogen derivative, which is isolated and then dissolved in organic solvent, (ref. paragraph 2a.1), and treated with silver nitrate. The global reaction scheme is the following:



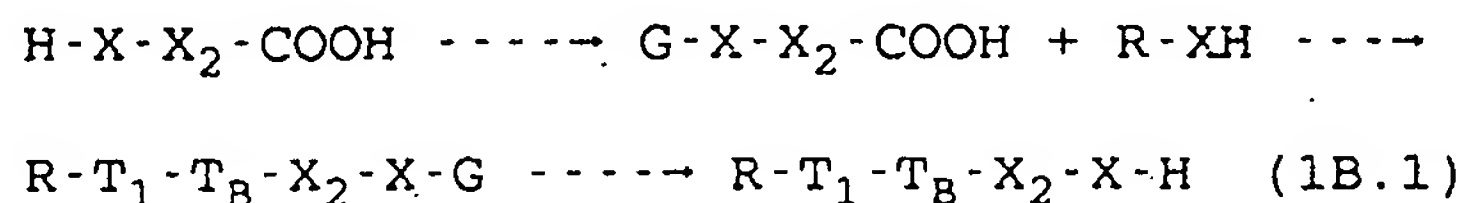
wherein T_1 , T_3 , X_2 , T_{B1} , T_C , Y are as above defined.

Alternatively, the halide $\text{Hal-X}_1\text{-COCl}$ can be used, wherein Hal is preferably bromine, which is reacted with the compound of formula (IA.2).

1b. When the drug precursor has the reactive function HX , wherein X is as above defined, instead of a carboxylic group, the two functional groups present on the precursor compound of B can be the following:

1b.1 A carboxylic group, which reacts with the HX function of the drug precursor, and a HX group, the latter reactive group of the precursor compound of B being equal to or different from the functional group of the drug precursor. The formula of the precursor compound of B is of the H-X-

X_2 -COOH type, wherein X and X_2 are as above defined. The H-X- function of the precursor compound of B is protected according to the known prior art methods and the carboxyl group is reacted, as above mentioned, according to the following scheme:



At the end of the reaction the HX function of the precursor compound of B is restored.

1b.2 When the precursor compound of B contains two carboxylic groups, it is treated with an equimolar amount of an agent activating the carboxyl group under the conditions previously described in 1a.1, and then reacted with the reactive HX function of the drug precursor molecule. Possible other reactive functions of HX type present in the two compounds must be protected as previously mentioned. Lastly a compound of formula $\text{R-T}_1\text{-T}_B\text{-X}_2\text{-COOH}$ (1B.2) is obtained.

2b. Nitroxyderivative synthesis.

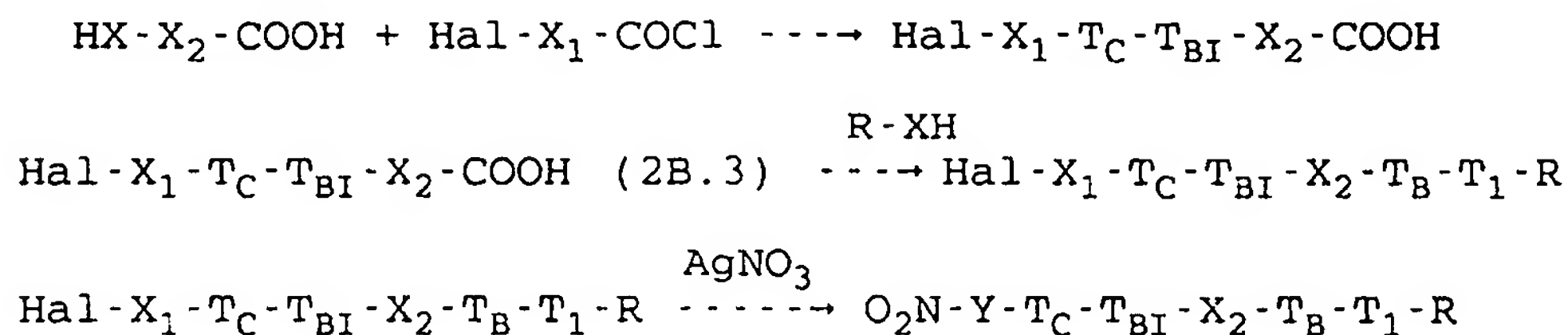
2b.1 To obtain the final nitroxyderivative starting from the compound of formula $\text{R-T}_1\text{-T}_B\text{-X}_2\text{-X-H}$ (1B.1), obtained at the end of the synthesis described in 1b.1, the (1B.1) compound is reacted with an halogenacid of formula $\text{Hal-X}_1\text{-COOH}$ which has been treated as previously described in paragraph 1a.1, or with the corresponding halogenacid

chloride. The resulting compound is dissolved in organic solvent, for example acetonitrile or tetrahydrofuran and reacted with silver nitrate.

2b.2 To obtain the final nitroxyderivative starting from the compound of formula $R-T_1-T_B-X_2-COOH$ (1B.2), obtained at the end of the synthesis described in 1b.2, the acid is transformed into the corresponding sodic salt, it is reacted with a $R_4-X_1-R_3$ compound, previously defined in the reaction A. scheme of paragraph 2a.1, obtaining according to the same process therein mentioned the final nitroxyderivative. Alternatively, when X_1 is a linear C_4 alkyl, the acid (1B.2) is reacted with triphenylphosphine in the presence of an halogenating agent such as CBr_4 or N-bromosuccinimide in tetrahydrofuran and the resulting compound dissolved in organic solvent for example acetonitrile, tetrahydrofuran, is reacted with silver nitrate.

2b.3 Alternatively to the synthesis process according to 1b.1 and 2b.1, it is possible to react in a first step the HX-function of the precursor compound of B $HX-X_2-COOH$ with the acyl chloride of an halogenacid of formula $Hal-X_1-CO-Cl$, wherein Hal is preferably Br, and subsequently the carboxylic function of the so obtained compound, with the drug precursor R-HX. In the third and last step the -Hal group is substituted with $-ONO_2$ according to the process

described in 2b.1. The reaction scheme is the following:

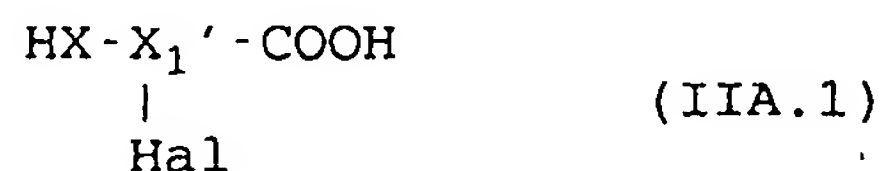


wherein T_C , T_{BI} , T_B , T_1 , X_2 , X_1 , Y are as above defined.

In the previous scheme the nitration can alternatively be carried out on the acid compound of formula (2B.3).

B) Synthesis of compounds of formula (II).

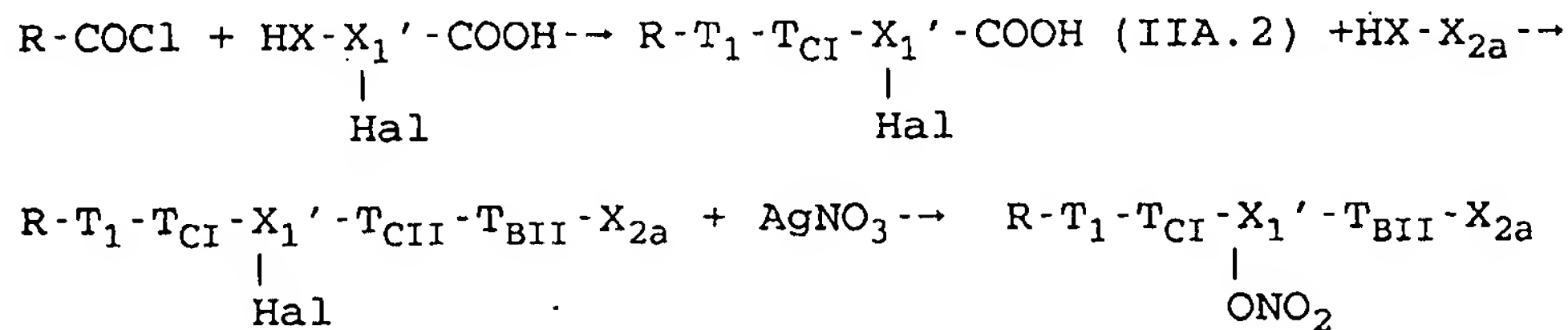
1a. When the drug precursor is of formula $R\text{-COOH}$ and the precursor compound of B_1 contains only one functional reactive group of formula XH , X being as above defined, $R\text{-COOH}$ is initially converted into the corresponding acyl-halide, or treated with an agent activating the carboxyl group as described in 1a.1, and then reacted with the HX function of an halogen-acid compound, said function being equal to or different from that present on the precursor compound of B_1 , said halogen-acid having the formula:



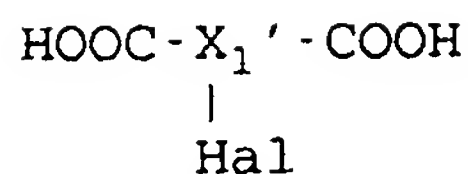
wherein X_1' is Y' as above defined without the oxygen atom through which the $-\text{NO}_2$ group is linked, X and Hal are as above defined.

The compound (IIA.1) can be obtained with the known method of the prior art. For example when $X = \text{NH}$, it can be

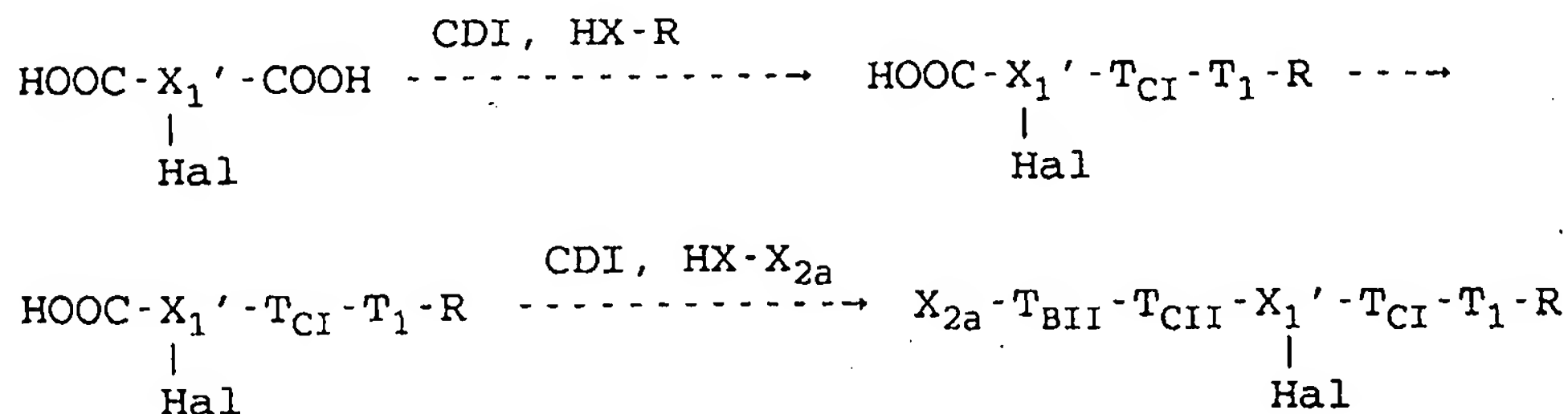
obtained from the corresponding hydroxy-aminoacid, protecting the aminic group by the corresponding ter-butyloxycarbonyl derivative and transforming the hydroxyl function into halogen group as described for the halogenation of the compound (1A.1b) in 2a.1. The free carboxylic function of the compound resulting from the reaction with the molecule of the drug precursor is reacted with the function present in the molecule of the precursor compound of B₁, as previously illustrated in 1a.1 for the reaction between the R-COOH acid and the precursor compound of B. In the final step the halogen atom (Hal) present on the radical X'₁ is substituted with an ONO₂ group by adding AgNO₃ to an organic solution of the compound. The reaction scheme is the following, exemplified starting from the RCOCl acid halide:



- 1b. When the drug precursor and the precursor compound of B₁ contain each a reactive group of general formula XH, the two groups in each of the two molecules being equal to or different from each other, wherein X is as above defined, the synthesis is carried out starting from an halogendiacid compound of formula



X_1' being as above defined, said compound being prepared from the corresponding hydroxy-diacid as described for the halogenation of the compound (1A.1b) in 2a.1. The halogendiacid compound is treated with an equimolar amount of an agent activating the carboxyl group, under the conditions previously described in 1a.1., and then it is reacted with the reactive function of the drug precursor molecule. In the subsequent step the second carboxylic function is treated with an activating agent, as previously made for the first, and reacted with the precursor compound of B_1 according to the following scheme:



The halogen atom is then substituted with the ONO_2 group as above mentioned.

3. Synthesis of the nitroso ($s=1$) derivatives of formula (I).

3a.1 The compound of formula (1A.1b) wherein $\text{R}_3 = \text{OH}$ is reacted with sodium nitrite in a solvent formed of a mixture of water with tetrahydrofuran in the presence of hydrochloric

acid. The reaction is widely illustrated in the prior art.

The general scheme is the following:



3a.2 When the compound obtained at the end of step A in 1a.2 has formula (IA.2) the corresponding nitroso derivative is obtained by treating an hydroxyacid of formula $HO-X_1-COOH$, X_1 being as above defined, first with an agent activating the carboxyl group, as described in 1a.1, then reacting it with 1A.2 and the resulting product with sodium nitrite as described in 3a.1.

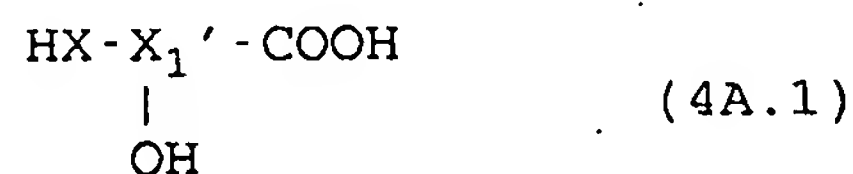
3b.1 To obtain the nitroso derivative starting from the compound of formula $R-T_1-T_B-X_2-XH$ (1B.1) obtained at the end of the synthesis described in 1b.1, the compound (1B.1) is reacted with an hydroxyacid as described in 3a.2.

3b.2 To obtain the nitroso derivative from the compound of formula $R-T_1-T_B-X_2-COOH$ (1B.2) obtained at the end of the synthesis described in 1b.2, the acid is transformed into the sodic salt and reacted with a compound $Hal-X_1-OH$, as previously described, and the obtained alcohol is treated as described in 3a.1.

4) Synthesis of the nitroso derivatives of formula (II)

4a.1 When the drug is of formula $R-COOH$ and the precursor compound of B_1 contains only one function reactive group of formula XH , X being as above defined, $R-COOH$ is ini-

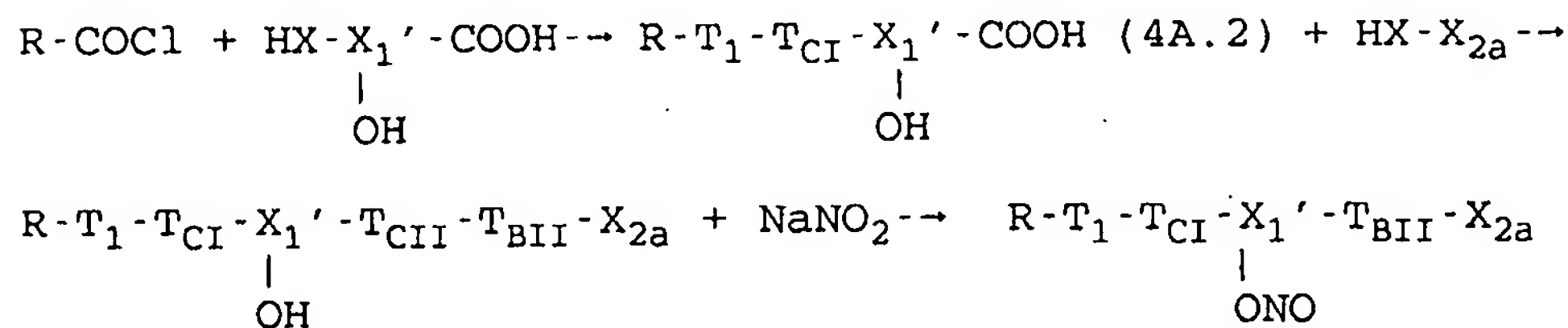
tially converted into the corresponding acyl-halide or treated with an agent activating the carboxyl group as described in 1a.1, and then reacted with the HX function of an hydroxy-acid compound, said function being equal to or different from that present on the precursor compound of B₁, said hydroxy-acid having the formula:



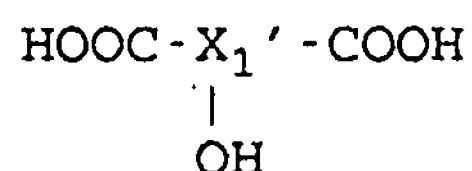
wherein X₁' is Y' as above defined without the oxygen atom through which the -NO group is linked, X is as above defined.

The free carboxylic function of the compound resulting from the reaction with the drug molecule is reacted with the function present in the molecule of the precursor compound of B₁, as previously illustrated in 1a.1 for the reaction between the R-COOH acid and the precursor compound of B. In the final step the alcohol is transformed into the nitroso-derivative as described in 3a.1.

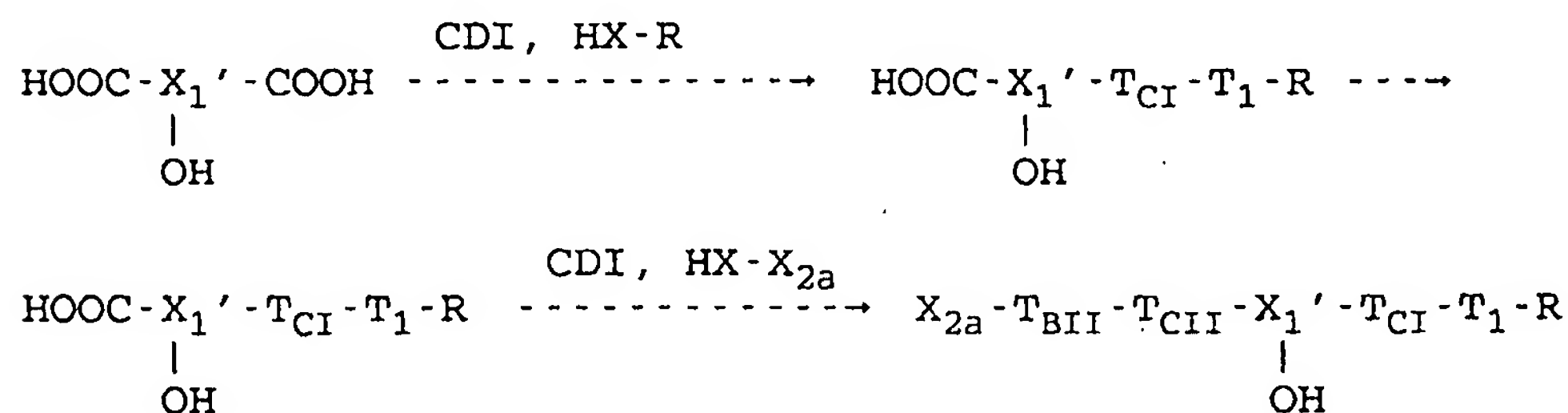
The reaction scheme is the following, exemplified starting from the RCOCl acid halide:



4b. When the drug and the precursor compound of B₁ contain each a reactive group of general formula XH, the two groups in each of the two molecules being equal to or different from each other, wherein X is as above defined, the synthesis is carried out starting from an hydroxydiacid compound of formula



X₁' being as above defined, said hydroxydiacid compound is treated with an equimolar amount of an agent activating the carboxyl group, under the conditions previously described in 1a.1., and then it reacted with the reactive function of the drug molecule. In the subsequent step the second carboxylic function is treated with an activating agent, as previously made for the first one, and reacted with the precursor compound of B₁ according to the following scheme:



The obtained compound is reacted as described in 3a.1.

The compounds object of the present invention are formulated in the corresponding pharmaceutical compositions for parenteral, oral and topic use according to the well known

methods in the art, together with the usual excipients; see for example the volume "Remington's Pharmaceutical Sciences 15a Ed."

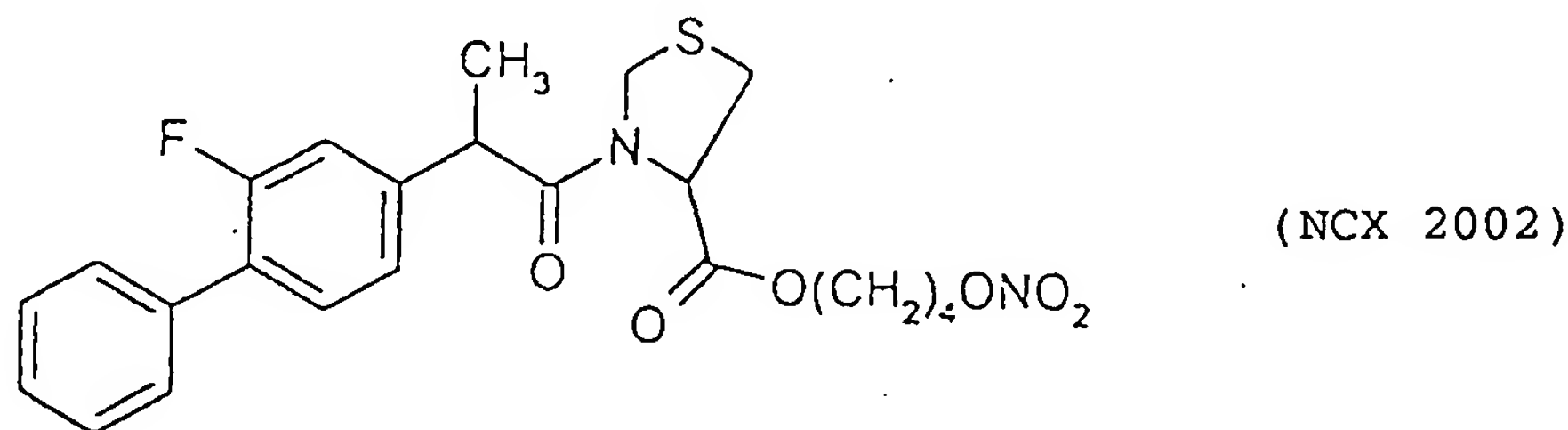
The amount on molar basis of the active principle in these formulations is the same, or lower, in comparison with that used of the corresponding precursor drug.

The daily administrable doses are those of the precursor drugs, or optionally lower. The daily doses can be found in the publications of the field, such as for example in "Physician's Desk reference".

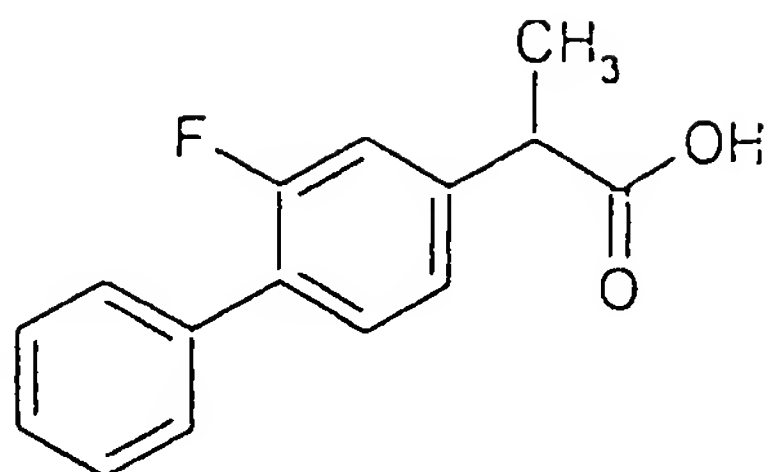
The following examples have the purpose to illustrate the invention and are not to be considered as limitative of the same.

EXAMPLE 1

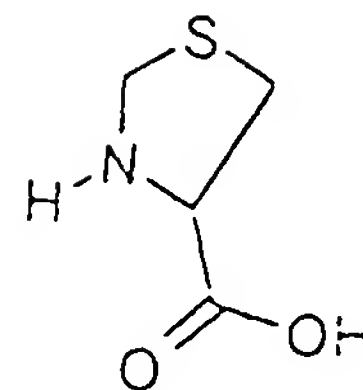
Synthesis of the 3-[2-fluoro- α -methyl-(1,1'-biphenyl)-4-acetyl]thiazolidin-4-carboxylic acid 4-(nitroxy)butyl ester (NO-Flurbiprofen), compound NCX 2002



starting from flurbiprofen (formula IX) and the precursor of B is (L)-4-thiazolidin carboxylic acid (formula PIV)



(IX)



(PIV)

a) Synthesis of 3-[2-fluoro- α -methyl-(1,1'-biphenyl)-4-acyl]thiazolidin-4-carboxylic acid

To a solution of 2-fluoro- α -methyl-(1,1'-biphenyl)-4-acetic acid (10 g, 41 mmol) in toluene (100 ml) and N,N-dimethylformamide (10 ml) cooled at 0°C, oxalylchloride (3.52 ml, 82 mmol) is added. After 2 hours at room temperature, the solution is evaporated at reduced pressure. The obtained residue is dissolved in acetone (50 ml) and the solution is added to a solution of 4-thiazolidinecarboxylic acid (5.44 g, 41 mmol) and triethylamine (14.9 ml, 106 mmol) in acetone (50 ml) cooled at 0°C. After 2 hours the solution is acidified with HCl 4 N, concentrated under vacuum, the residue is treated with ethyl acetate and the organic phase is washed first with HCl 2 N, then with water. The organic phase is anhydriified with sodium sulphate and evaporated at reduced pressure. By crystallization with ethyl acetate/n-hexane 9.4 g of the expected product in the form of a white solid having m.p. 142°C-147°C, is obtained.

$^1\text{H-NMR}$ (CDCl_3): 7.74-7.62 (4H, m), 7.35 (2H, t), 7.18-7.13 (2H, m), 5.06 (1H, m), 4.63 (1H, d), 4.42 (1H, d), 4.14

(1H, q), 3.13 (2H, m), 1.53 (3H, d).

b) Synthesis of the 3-[2-fluoro- α -methyl-(1,1'-biphenyl)-4-acetyl]thiazolidin-4-carboxylic acid 4-(bromobutyl) ester

To a solution of the acid obtained in the previous step a) (9.43 g, 26.24 mmol) in tetrahydrofuran (150 ml) triphenylphosphine (13.76 g, 52.49 mmol) and carbon tetrabromide (17.4 g, 52.49 mmol) are added. The reaction mixture is let under stirring for 24 hours at room temperature. The solvent is removed by evaporation at reduced pressure. The obtained crude product is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 2.25 g of the ester are obtained in an oil form.

c) Synthesis of the 3-[2-fluoro- α -methyl-(1,1'-biphenyl)-4-acetyl]thiazolidin-4-carboxylic acid 4-(nitroxy)butyl ester

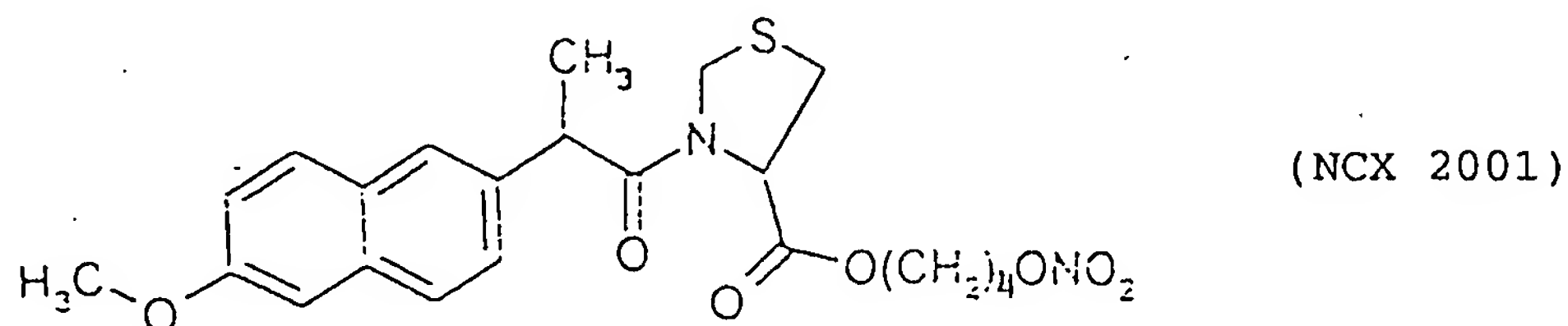
To a solution of the ester obtained at the end of the previous step (2.6 g, 5.26 mmol) in acetonitrile (20 ml) silver nitrate (1.07 g, 6.3 mmol) is added. The reaction mixture is heated for 4 hours under reflux away from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 0.84 g of the 3-[2-fluoro- α -methyl-(1,1'-biphenyl)-4-acetyl]thiazolidin-4-carboxylic acid 4-(nitroxy)butyl ester are obtained in an oil form.

$^1\text{H-NMR}$ (CDCl_3): 7.56-7.09 (8H, m), 5.77 (1H, dd), 4.67

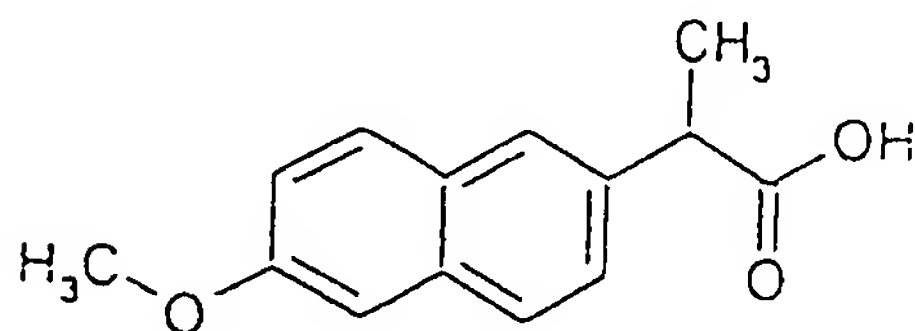
(2H, d), 4.51 (2H, t), 4.24 (2H, t), 4.15 (1H, q), 3.30-3.17 (2H, m), 1.74-1.70 (4H, m), 1.52 (3H, d).

EXAMPLE 2

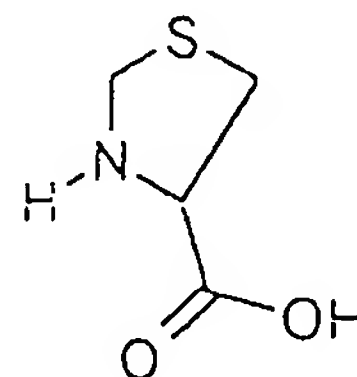
Synthesis of the 3-(6-methoxy- α -methyl-2-naphthalenacetyl)thiazolidin-4-carboxylic acid 4-(nitroxy)butyl ester (NO-Naproxene) (NCX 2001)



starting from naproxene (formula VI) and the precursor of B is (L)-4-thiazolidin carboxylic acid (formula PIV)



(VI)



(PIV)

a) Synthesis of the 3-(6-methoxy- α -methyl-2-naphthalenacetyl)thiazolidin-4-carboxylic acid

To a solution of 6-methoxy- α -methyl-2-naphthalenacetic acid (4.02 g, 17.5 mmoles) in toluene (30 ml) and N,N-dimethylformamide (0.3 ml) cooled at 0°C, oxalylchloride (2.92 ml,

34.06 mmol) is added. After 2 hours at room temperature, the solution is evaporated at reduced pressure. The obtained residue is dissolved in acetone (50 ml) and the solution is added to a solution of 4-thiazolidinecarboxylic acid (2.33 g, 17.5 mmol) and triethylamine (6.34 ml, 45.5 mmol) in acetone (50 ml) cooled at 0°C. After 2 hours the solution is acidified with HCl 4 N, concentrated under vacuum, the residue is treated with ethyl acetate and the organic phase is washed first with HCl 2 N, then with water. The organic phase is anhydri-fied with sodium sulphate and evaporated at reduced pressure. 4.43 g of the expected product are obtained in the form of a white solid having m.p. 165°C-168°C.

¹H-NMR (CDCl₃): 7.75-7.66 (3H, m), 7.34 (1H, d), 7.14-7.11 (2H, m), 5.14 (1H, m), 4.80-4.61 (2H, m), 4.07 (1H, q), 3.91 (3H, s), 3.30-3.23 (2H, m), 1.53 (3H, d).

b) Synthesis of the 3-(6-methoxy- α -methyl-2-naphthalenacetyl)thiazolidin-4-carboxylic acid 4-(bromobutyl) ester

To a solution of the acid obtained in the previous step a) (4 g, 11.6 mmol) in tetrahydrofuran (50 ml) triphenylphosphine (6.07 g, 23.1 mmol) and carbon tetrabromide (7.66 g, 23.2 mmol) are added. The reaction mixture is left under stirring for 24 hours at room temperature. The solvent is removed by evaporation at reduced pressure. The obtained crude product is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 2.25 g of the

ester are obtained in an oil form.

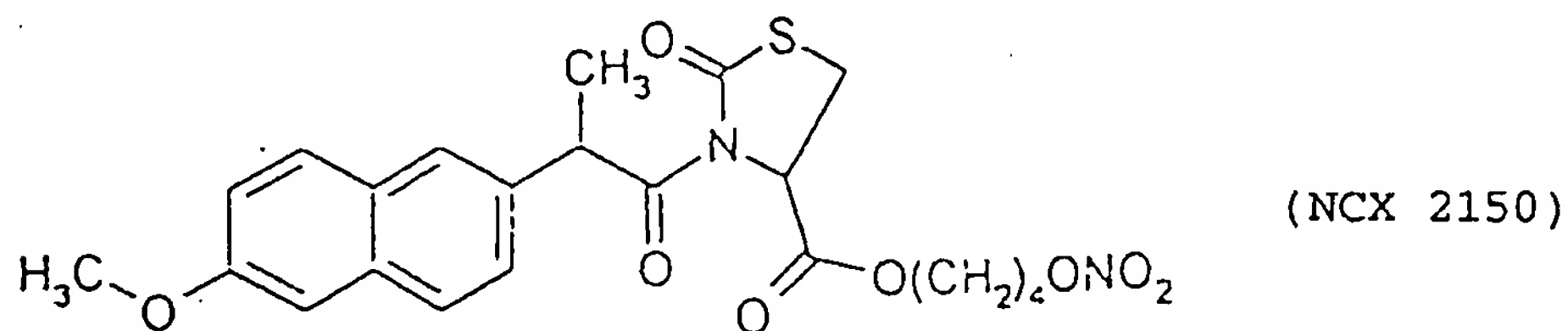
c) Synthesis of the 3-(6-methoxy- α -methyl-2-naphthalenacetyl)thiazolidin-4-carboxylic acid 4-(nitroxy)butyl ester

To a solution of the ester obtained at the end of the previous step (2 g, 4.16 mmol) in acetonitrile (20 ml) silver nitrate (0.85 g, 5 mmol) is added. The reaction mixture is heated for 5 hours under reflux away from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 0.99 g of the 3-(6-methoxy- α -methyl-2-naphthalenacetyl)thiazolidin-4-carboxylic acid 4-(nitroxy)butyl ester are obtained in an oil form.

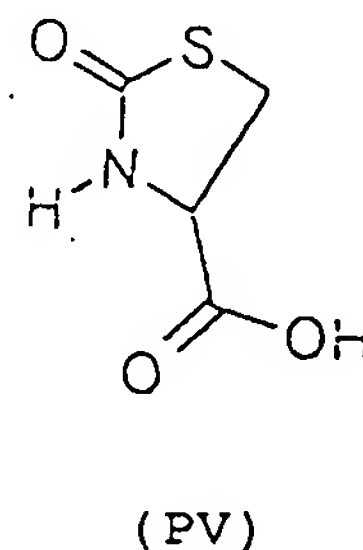
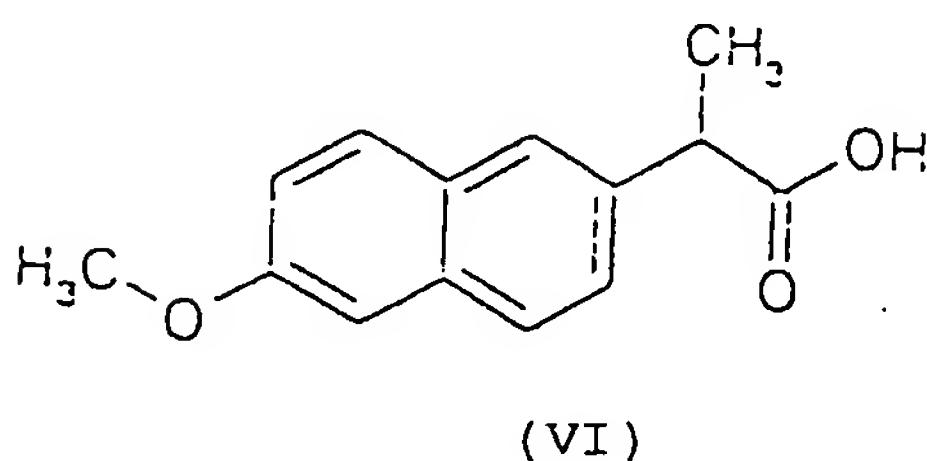
$^1\text{H-NMR}$ (CDCl_3): 7.66 (3H, m), 7.38 (1H, m), 7.15 (2H, m), 5.06 (1H, dd), 4.66 (2H, d), 4.51 (2H, t), 4.25 (2H, t), 3.98 (1H, q), 3.92 (3H, s), 3.13 (2H, d), 1.84 (4H, m), 1.53 (3H, d).

EXAMPLE 3

Synthesis of the 3-(6-methoxy- α -methyl-2-naphthalenacetyl)-(R)-2-oxothiazolidin-4-carboxylic acid 4-(nitroxy) butyl ester (NCX 2150)



starting from naproxene (formula VI) and the precursor of B is (L)-2-oxo-4-thiazolidin carboxylic acid (formula PV)



a) synthesis of the 3-(6-methoxy- α -methyl-2-naphthalenacetyl)-(R)-2-oxothiazolidin-4-carboxylic acid

To a solution of 6-methoxy- α -methyl-2-naphthalenacetic acid (7.0 g, 30.4 mmol) in toluene (100 ml) and N,N-dimethylformamide (10 ml) cooled at 0°C, oxalylchloride (5.23 ml, 61 mmol) is added. After 2 hours at room temperature the solution is evaporated at reduced pressure. To the solution of the obtained residue dissolved in tetrahydrofuran (50 ml) a mixture is added consisting of 2-oxothiazolidin-4-carboxylic acid (4.07 g, 27.6 mmol), 4-dimethylaminopyridine (0.84 g, 6.9 mmol), triethylamine (7.69 ml, 55.2 mmol) in tetrahydrofuran (50 ml) cooled at -10°C. The mixture is left at room temperature for 24 hours. The reaction mixture is washed with HCl 5%, then with water. The organic phase is anhydri-fied with sodium sulphate and then evaporated at reduced pressure.

The obtained residue is purified by chromatography on silica gel eluting with methylene chloride/methanol 95/5. 6.79 g of the expected product are obtained in the form of an amorphous solid.

b) Synthesis of the 3-(6-methoxy- α -methyl-2-naphthalenacetyl)-(R)-2-oxothiazolidin-4-carboxylic acid 4-(bromobutyl) ester

To a solution of 3-(6-methoxy- α -methyl-2-naphthalenacetyl)-(R)-2-oxothiazolidin-4-carboxylic acid (6.79 g, 18.9 mmol) in tetrahydrofuran (100 ml) triphenylphosphine (9.91 g, 37.8 mmol) and carbon tetrabromide (12.53 g, 37.8 mmol) are added. The reaction mixture is left under stirring for 16 hours at room temperature, then the solvent is removed by evaporation at reduced pressure. The obtained crude product is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 1.83 g of the ester are obtained in the form of an oil.

c) Synthesis of the 3-(6-methoxy- α -methyl-2-naphthalenacetyl)-(R)-2-oxothiazolidin-4-carboxylic acid 4-(nitrobutyl) ester

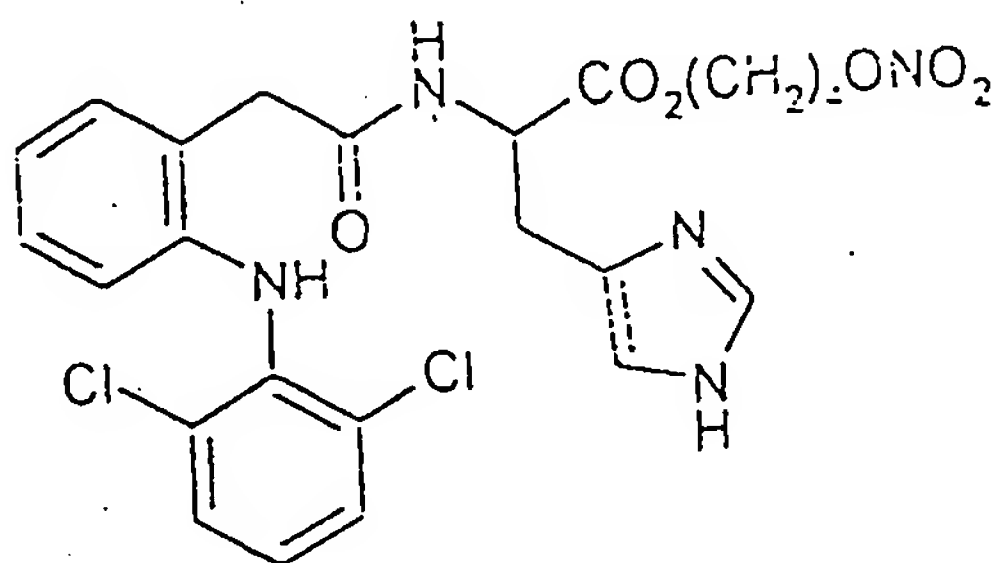
To a solution of the ester obtained at the end of the previous step (1.7 g, 3.44 mmol) in acetonitrile (20 ml) silver nitrate (0.82 g, 4.81 mmol) is added. The reaction mixture is heated for 6 hours under reflux away from light. The formed salt is removed by filtration and the solution is evaporated under pressure. The obtained residue is purified by

chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 0.77 g of 3-(6-methoxy- α -methyl-2-naphthalenace-tyl)-(R)-2-oxothiazolidin-4-carboxylic acid 4-(nitroxy)butyl ester are obtained in an oil form.

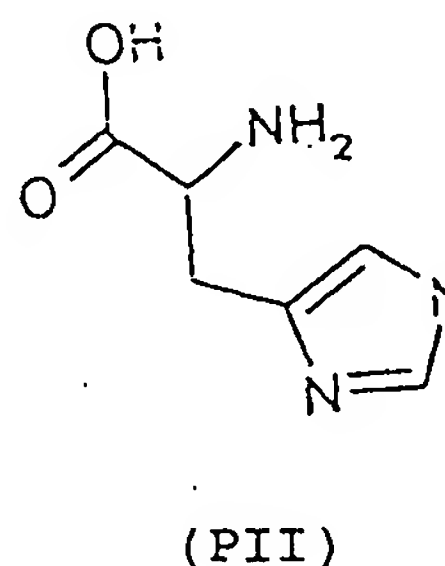
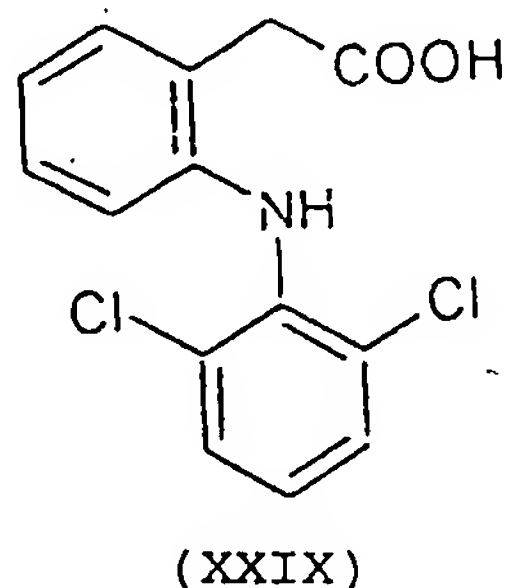
$^1\text{H-NMR}$ (CDCl_3): 7.74-7.67 (3H, m), 7.47 (1H, m), 7.14-7.10 (2H, m), 5.28 (1H, dd), 4.12-3.91 (5H, m), 3.90 (3H, s), 3.63 (1H, dd), 3.33 (1H, dd), 1.55 (3H, d), 1.30-1.23 (4H, m).

EXAMPLE 4

Synthesis of [2-[(2,6-dichlorophenyl)amino]benzeneacetyloxy]-(L)-histidine 4-(nitroxy)butyl ester



wherein the precursor drug of the invention compound is diclofenac of formula (XXIX) and the precursor compound of B is (L)-histidine of formula (PII):



a) synthesis of [2-[(2,6-dichlorophenyl)amino]benzeneacety-

loxy] (L)-histidine

To a diclofenac solution (3 g, 10.13 mmol) in tetrahydrofuran (50 ml) cooled at 0°C, 1,1'-carbonyldiimidazole (1.69 g, 10.13 mmol) is added under stirring. After 10 minutes the solution is treated with (L) histidine (1.57 g, 10.13 mmol) and left under stirring at room temperature for 4 hours. The reaction mixture is concentrated under vacuum, treated with methylene chloride and then washed in sequence with HCl 1% and then with water. The organic phase is anhydriified with sodium sulphate and evaporated under vacuum. The obtained residue is purified by chromatography on silica gel column, eluting with ethyl acetate. [2-[(2,6-dichlorophenyl)amino] benzeneacetyloxy] (L)-histidine is obtained.

b) Synthesis of [2-[(2,6-dichlorophenyl)amino]benzeneacetyloxy] (L)-histidine 4-bromobutyl ester

To a solution of [2-[(2,6-dichlorophenyl)amino]benzeneacetyloxy] (L)-histidine (5 g, 11.54 mmol) in tetrahydrofuran (100 ml) triphenylphosphine (9.08 g, 34.62 mmol) and carbon tetrabromide (11.48 g, 34.62 mmol) are added under stirring. The reaction mixture is left at room temperature for 24 hours, then the solvent is removed by evaporation at reduced pressure. The obtained crude product is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 1/1. (S)-[2-[(2,6-dichlorophenyl)amino]benzeneacetyloxy] (L)-histidine 4-

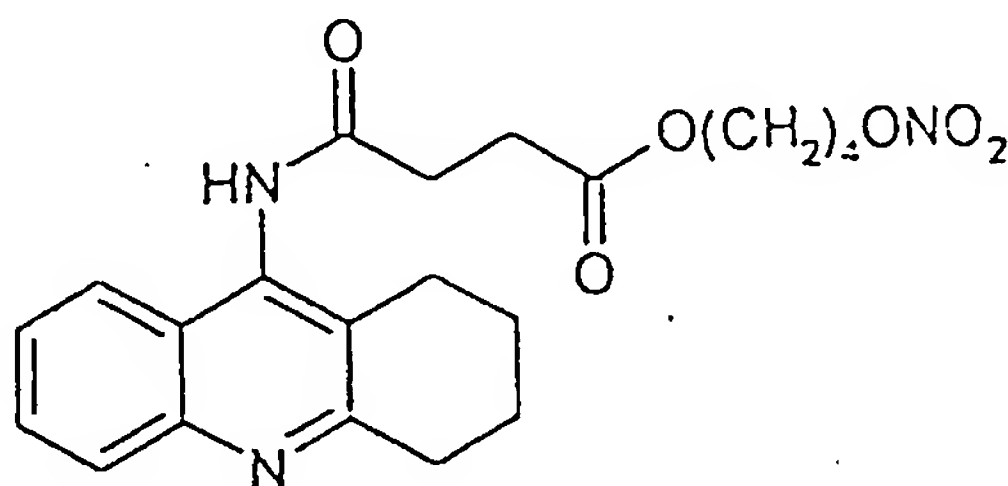
bromobutyl ester is obtained.

c) Synthesis of [2-[(2,6-dichlorophenyl)amino]benzeneacetyloxy] (L)-histidine 4-nitroxybutyl ester

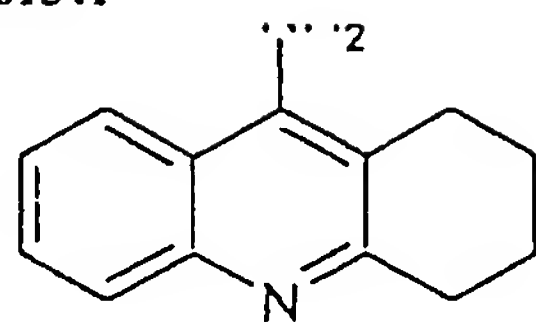
To a solution of [2-[(2,6-dichlorophenyl)amino]benzeneacetyloxy] (L)-histidine 4-bromobutyl ester (3 g, 5.28 mmoles) in acetonitrile (30 ml) silver nitrate (1.79 g, 10.56 mmoles) is added. The reaction mixture is heated under reflux for 6 hours sheltered from the light, the formed salt is removed by filtration and the solution is evaporated under reduced pressure. The obtained residue is purged by chromatography on silica gel column eluting with n-hexane/ethyl acetate 1/1. [2-[(2,6-dichlorophenyl)amino]benzeneacetyloxy] (L)-histidine 4-nitroxybutylester is obtained. Yield 35%.

EXAMPLE 5

Synthesis of 5-[[4-oxo-(4-nitroxybutyloxy)butanoyl]amino]-1,2,3,4-tetrahydroacridine



wherein the precursor drug of the invention compound is tacrine of formula (XXXV) and the precursor compound of the bridging group B is succinic acid of formula (RI):



(XXXV)



(RI)

a) Synthesis of succinic acid 4-chlorobutyl monoester

To a solution of succinic anhydride (2 g, 19.98 mmol) in chloroform (30 ml), cooled at 0°C, N,N'-dicyclohexylcarbodiimide (4.2 g, 20.35 mmol) and 4-dimethylaminopyridine (100 mg, 0.8 mmol) are added under stirring. After 30 minutes 4-chlorobutanol (2.1 g, 19.35 mmol) is added. The reaction mixture is left at room temperature for 7 hours under stirring, then it is acidified with HCl 5% and it is extracted with ethyl acetate. The organic phase is washed with brine, anhydri-fied with sodium sulphate and evaporated at reduced pressure. The crude product is purified by chromatography on silica gel column eluting with methylene chloride/methanol 8/2. Succinic acid 4-chlorobutyl monoester is obtained.

b) Synthesis of 5-[[4-Oxo-(4-chlorobutyloxy)butanoyl]amino]-1,2,3,4-tetrahydroacridine

To a solution of succinic acid 4-chlorobutyl monoester (2.9 g, 10.02 mmol) in N,N-dimethylformamide (30 ml), cooled at 0°C, N,N'-dicyclohexylcarbodiimide (2.2 g, 10.66 mmol) and 4-dimethylaminopyridine (100 mg, 0.8 mmol) are added under stirring. After 5 minutes tacrine (2 g, 10.08 mmol) is added. The reaction mixture is left at room temperature for 24 hours, then acidified with HCl 5% and extracted with ethyl acetate.

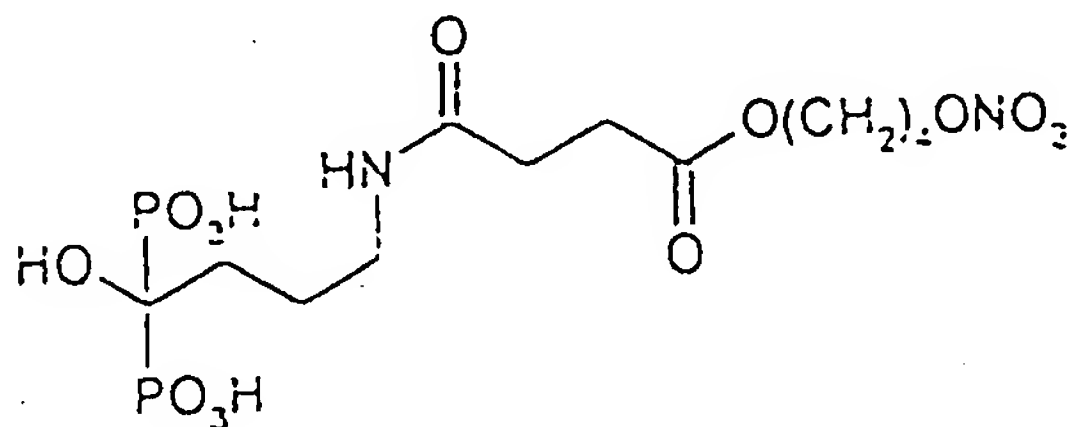
The organic phase is washed with brine, anhydriified with sodium sulphate and evaporated at reduced pressure. The crude product is purified by chromatography on silica gel eluting with methylene chloride/methanol 8/2. 5-[[4-oxo-(4-chlorobutyloxy)-butanoyl]amino]-1,2,3,4-tetrahydroacridine is obtained.

c) synthesis of 5-[[4-Oxo-(4-nitroxybutyloxy)butanoyl]amino]-1,2,3,4-tetrahydroacridine

To a solution of 5-[4-oxo-(4-chlorobutyloxy)butanoyl]-amino]-1,2,3,4-tetrahydroacridine (3 g, 7,71 mmols) in acetonitrile (50 ml) silver nitrate (1.79 g, 10.56 mmols) is added under stirring. The reaction mixture is heated under reflux for 36 hours away from light, the formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel column eluting with ethyl acetate. 5-[[4-oxo-(4-nitroxybutyloxy)butanoyl]amino]-1,2,3,4-tetrahydroacridine is obtained. Yield 27%.

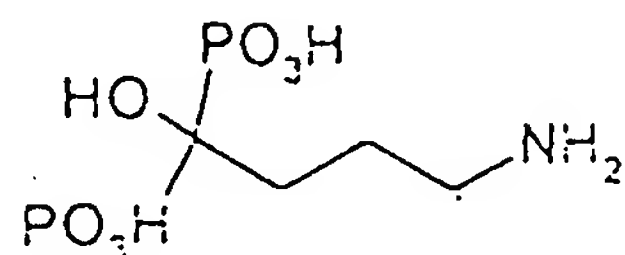
EXAMPLE 6

Synthesis of [4-amino-[4-oxo-(4-nitroxybutyloxy)butanoyl]-1-hydroxybutyliden] biphosphonic acid



wherein the precursor drug of the invention compound is

alendronic acid of formula (XXXVI) and the precursor compound of the bridging group B is succinic acid of formula (RI):



(XXXVI)

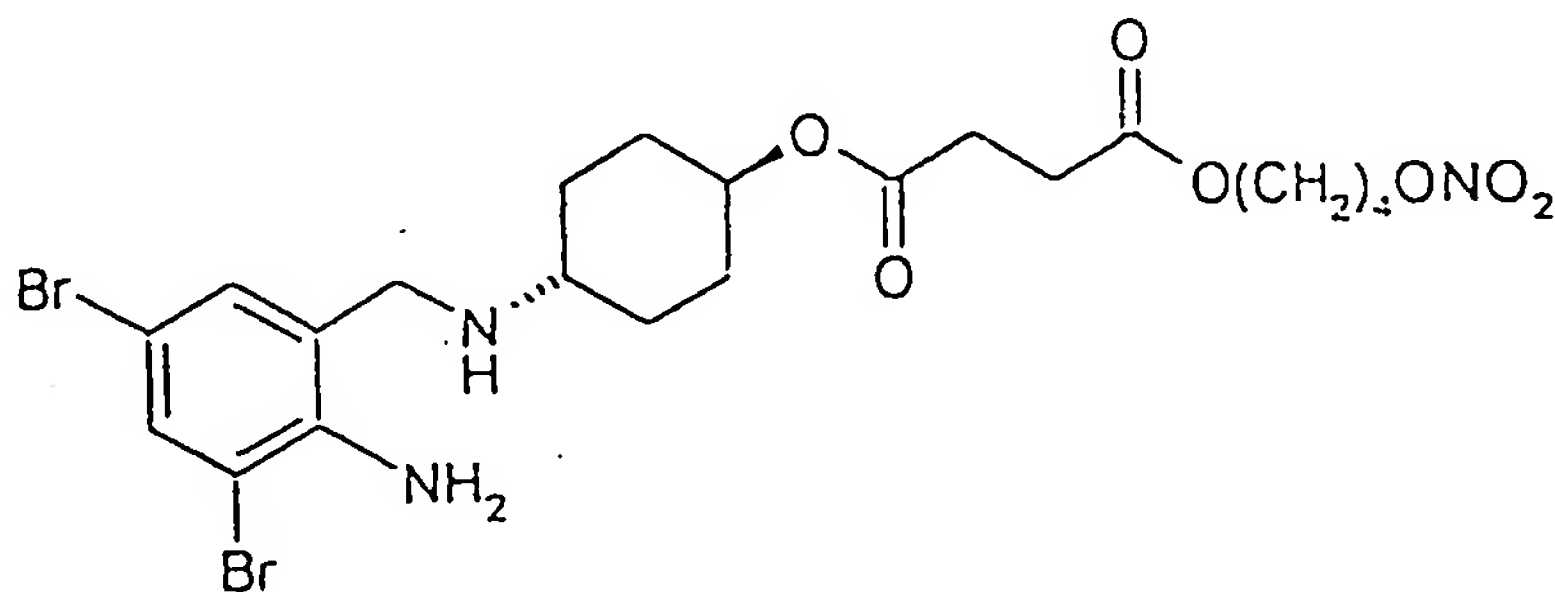


(RI)

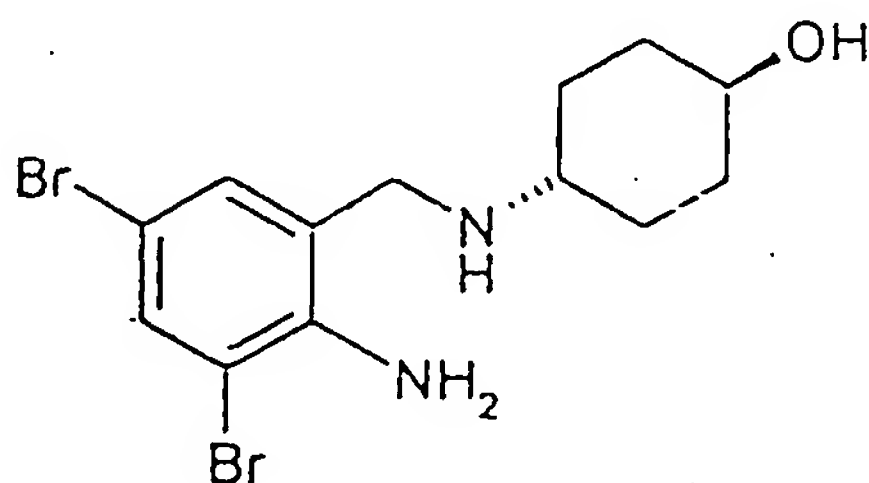
The compound is synthesized following the synthesis procedure reported in Example 5. Yield 19%.

EXAMPLE 7

Synthesis of [4-oxo-(4-nitroxybutyloxy)butanoyl 4-(2-amino-3,5-dibromophenyl)-methylamino] cyclohexanol ester



wherein the precursor drug of the invention compound is am-broxol of formula (XII) and the precursor compound of the bridging group B is succinic acid of formula (RI):



(XII)



(RI)

a) Synthesis of 4-[(2-Tert-butoxycarbonylamino-3,5-dibromophenyl)methylamino] trans cyclohexanol

To a mixture of 4-[(2-amino-3,5-dibromophenyl)methylamino]cyclohexanol (5 g, 13.22 mmols) in dioxane (35 ml) and water (50 ml), triethylamine (3.31 ml, 23.7 mmols) and di-tert-butyl dicarbonate (3.46 g, 15.86 mmols) are added under stirring. After 24 hours the solution is concentrated under vacuum, treated with HCl 1% until having neutral pH in the solution, and it is extracted with ethyl acetate. The organic phase is anhydrified with sodium sulphate and evaporated under vacuum. 4-[(2-tert-butoxycarbonylamino-3,5-dibromophenyl) methyl amino]cyclohexanol is obtained which is used without further purification.

b) Synthesis of [4-Oxo-(4-chlorobutyloxy)butanoyl]-4-(2-tert-butoxycarbonylamino-3,5-dibromophenyl) methylamino] cyclohexanol ester

To a solution of succinic acid 4-chlorobutyl monoester (4 g, 19.18 mmoli) in tetrahydrofuran (40 ml), 1,1'-carbonyldiimidazol (3.4 g, 20.96 mmols) is added under stirring. After 10 minutes the solution is treated with 4-[(2-tert-butoxycarbonylamino-3,5-dibromophenyl) methyl amino]cyclohexanol (9.8 g, 20.5 mmols) and it is left at room temperature for 4 hours. The reaction mixture is concentrated under vacuum, treated with methylene chloride, washed with HCl 1% and then with water. The organic phase is anhydrified with sodium sulphate

and evaporated under vacuum. The obtained residue is purified by chromatography on silica gel column, eluting with n-hexane/ethyl acetate 1/1. [4-oxo-(4-chlorobutyloxy)butanoyl-4-(2-tert-butoxycarbonylamino-3,5-dibromophenyl) methylamino] cyclohexanol ester is obtained.

c) Synthesis of [4-Oxo-(4-nitroxybutyloxy)butanoyl-4-(2-tert-butoxycarbonylamino-3,5-dibromophenyl) methylamino] cyclohexanol ester

To a solution of [4-oxo-(4-chlorobutyloxy)butanoyl-4-(2-tert-butoxycarbonylamino-3,5-dibromophenyl) methylamino] cyclohexanol ester (4 g, 5.98 mmol) in acetonitrile (70 ml) silver nitrate (1.5 g, 8.83 mmol) is added under stirring. The reaction mixture is heated under reflux for 24 hours away from light, the formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. [4-oxo-(4-nitroxybutyloxy)butanoyl-4-(2-tert-butoxycarbonylamino-3,5-dibromophenyl) methylamino] cyclohexanol ester is obtained.

d) synthesis of [4-[4-Oxo-(4-nitroxybutyloxy)butanoyl](2-amino-3,5-dibromophenyl) methylamino] cyclohexanol ester

To a solution of [4-oxo-(4-nitroxybutyloxy)butanoyl-4-(2-tert-butoxycarbonylamino-3,5-dibromophenyl) methylamino] cyclohexanol ester (3.2 g, 4.6 mmol) in ethyl acetate (50 ml), cooled at 0°C, ethyl acetate/HCl 5N (6.5 ml) is added

under stirring. The solution is left at 0°C for 4 hours, the precipitate is filtered. The obtained crude product is treated with ethyl acetate and with 5% sodium bicarbonate, then with water. The organic phase is anhydriified with sodium sulphate and evaporated at reduced pressure. [4-oxo-(4-nitroxybutyloxy)butanoyl-4-(2-amino-3,5-dibromo phenyl) methylamino] cyclohexanol ester is obtained. Yield 17%.

PHARMACOLOGICAL TESTS

EXAMPLE

Acute Toxicity

Acute toxicity has been evaluated by administering to a group of 10 rats weighing 20 g a single dose of each of the tested compounds, by cannula, by os in an aqueous suspension of carboxymethylcellulose 2% w/v.

The animals are kept under observation for 14 days. In no animal of the group toxic symptoms appeared even after administration of a 100 mg/Kg dose.

EXAMPLE F1

Test 1 - experimental model in vivo with N-ethylmaleimide (NEM): study of the gastric tolerability of some drugs screened as precursors of the compounds of the invention.

The animals (rats, weight about 200 g) are distributed in the following groups (No. 10 animals for group):

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v

of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, physiologic solution when by parenteral route),

2° group: treatment: carrier + NEM,

B) Groups administered with each drug:

group I: treatment: carrier + drug,

group II: treatment: carrier + drug + NEM.

The drugs assayed in this experiment are the following (Table I): indomethacin, ambroxol, mesalamine, sodic alendronate, tacrine, omeprazol, misoprostol.

Indomethacin, ambroxol and alendronate are administered by os, mesalamine by intracolonic (rectal) route and tacrine, omeprazol, misoprostol by subcutaneous route.

The maximum tolerated dose, determined by administering each substance by the above said routes to the animals not treated with NEM, is reported in Table I. With higher doses than those reported in the Table, enteropathy, diarrhoea, depression, tremor and sedation have appeared in the animals.

In this experimental model the animals are at first treated with NEM by subcutaneous injection at a dose of 25 mg/kg in physiologic solution. The drug is administered one hour later, in suspension in the carrier. Animals are sacrificed after 24 hours and evaluation of the damage to the gastrointestinal mucosa is made by counting the number of rats, inside each group, with lesions to the stomach at a visual

inspection. The total number of said rats is then divided by the total number of rats of the group and multiplied by 100. The thus obtained percentages are reported in Table I. The Table shows that in the groups of rats treated with said drugs without NEM, no gastric lesions were detectable.

All the rats of group II (treated with NEM) showed gastric lesions after administration with the following drugs: indomethacin, ambroxol, mesalamine, sodic alendronate, tacrine. Said drugs therefore can be used in the synthesis of the products of the invention.

Omeprazol and misoprostol cannot instead be used, on the basis of the results provided in test 1, for preparing the products of the invention.

EXAMPLE F2

Test 2 (in vitro): inhibition of apoptosis (DNA fragmentation) induced in the endothelial cells by CIP in the presence of some drugs screened as precursors of the compounds of the invention.

The following precursor drugs (Table II): indomethacin, paracetamol, clopidogrel, salbutamol, ambroxol, sodic alendronate, dipylline, cetirizine, enalapril, nicotinamide, ampicilline, aciclovir, mesalamine, tacrine, simvastine, omeprazol have been tested.

Human endothelial cells of the umbilical vein are prepared according to a standard method. Fresh umbilical veins are filled with a collagenase solution 0.1% by weight and

incubated at 37°C for 5 minutes.

Subsequently the veins are perfused with the medium M 199 (GIBCO, Grand Island, NY) pH 7.4 with 0.1% (weight/volume) of collagenase, added with 10% of bovine fetus serum (10 mcg/ml), sodium heparin (50 mcg/ml), thymidine (2.4 mcg/ml), glutamine (230 mcg/ml), penicillin (100 UI/ml), streptomycin (100 mcg/ml) and streptomycin B (0.125 mcg/ml). The cells are collected from the perfusate by centrifugation at 800 rpm and harvested in culture flasks T-75, pretreated with human fibronectin. Cells are then harvested in the same medium, added with bovine hypothalamic growth factor (100 ng/ml). When the cells of the primary cell culture (the cells directly removed from ex-vivo umbilical vein) form a single layer of confluent cells (about 8,000,000 cells/flask), harvesting is stopped and the layers are washed and trypsinized. The cellular suspensions are transferred into wells of a culture plate having 24 wells, half of said wells being added with the same culture medium containing the drug at a 10^{-6} M concentration, and harvested in a thermostat at 37°C at a constant moisture (90%), $\text{CO}_2 = 5\%$. When the drug is not soluble in the culture medium, it is formerly dissolved in a small amount of dimethylsulphoxide. The maximum amount of dimethylsulphoxide which can be added to the culture medium is 0.5%. Only the cells coming from these first subcultures are used for the tests with cumene hydroperoxide (CIP). The cells are identified

as endothelial cells by morphological examination and by the specific immunological reaction towards factor VIII; these cultures did never show contaminations from myocytes or fibroblasts.

Before starting the test, the cellular culture medium is removed and the cellular layers are carefully washed with a standard physiologic solution buffered with phosphate 0.1 M pH 7.0, at the temperature of 37°C. The content of each well is then incubated for one hour with a CIP suspension in the culture medium at a 5 mM concentration. Evaluation of the cellular damage (apoptosis) is carried out by determining the per cent variation of the DNA fragmentation in the cultures containing the drug + CIP with respect to the controls treated with CIP only. Said % variation of DNA fragmentation is determined by evaluating the fluorescence variation by a BX60 Olympus microscope (Olympus Co., Roma) set at the wave length of 405-450 nm, of the test samples with respect to the optical density of the controls. The fluorescence of each sample was determined on 5 replicates. Statistic evaluation has been made with t Student test ($p < 0.01$).

Results are given in Table II and show that indomethacin, paracetamol, clopidogrel, salbutamol, sodic alendronate, dipylline, cetirizine, enalapril, nicotinamide, ampicilline, aciclovir, tacrine, omeprazol do not significantly inhibit apoptosis; these drugs can therefore be used for preparing the

products of the invention.

On the contrary ambroxol, mesalamine and simvastatine inhibit apoptosis. Therefore on the basis of the results of test 2 these compounds could not be used for preparing the products of the invention.

EXAMPLE F3

Test 3 - experimental in vivo model with N^ω-nitro-L-arginine-methyl ester (L-NAME): gastric tolerability (gastrointestinal damage incidence), hepatic (GPT dosage, glutamic-pyruvic transaminase) and cardiovascular (blood pressure) tolerability of some drugs screened as precursors of the compounds of the invention.

The experimental model adopted is according to J. Clin. Investigation 90, 278-281, 1992.

The endothelial dysfunction is evaluated by determining the damage induced by L-NAME administration to the gastrointestinal mucosa, the hepatic damage (GPT increase), and the vascular endothelium or cardiovascular damage as blood hypertension.

The animals (rats, average weight 200 g) are divided in groups as herein below described. The group receiving L-NAME is treated for 4 weeks with said compound dissolved at the concentration of 400 mg/litre in drinking water. The following groups (No. 10 animals for group) are constituted:

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, physiologic solution when by parenteral route),

2° group: treatment: carrier + L-NAME,

B) Groups treated with the drug:

3° group: treatment: carrier + drug,

4° group: treatment: carrier + drug + L-NAME.

The drugs used in the test are paracetamol, doxorubicin, simvastatine, omeprazol and misoprostol. Each drug is administered once a day for 4 weeks.

The maximum tolerated dose of the drug being administered to the animals is determined by evaluating, in a separate dose scaling up experiment on untreated animals, the appearance in the animals of symptoms such as enteropathy, diarrhoea, depression, tremor, sedation.

At the end of the four weeks access to water is prevented and after 24 hours the animals are sacrificed.

One hour before the sacrifice blood pressure is determined and a blood pressure increase is taken as an indication of a damage being occurred to vascular endothelium.

The damage to the gastric mucosa is evaluated as previously mentioned in test 1 (ex. F1). The hepatic damage is determined by evaluation after the sacrifice of the glutamic-pyruvic transaminase (GPT increase).

The drug meets test 3 and it can therefore be used for preparing the compounds of the invention, when in the group of rats treated with L-NAME + drug + carrier, an higher hepatic damage (higher GPT values) and/or higher gastric damage and/or higher cardiovascular damage (higher blood pressure) are found in comparison with the group treated with the carrier only, or the group treated with carrier + drug, or the group treated with carrier + L-NAME.

The test results are reported in Table IV. The % gastric lesions have been determined as in Test 1. The % GPT and % blood pressure values are referred to the corresponding value found in the animals of the 1st group of the control groups. The average value of the blood pressure in this group was of 105 ± 8 mmHg.

The results obtained show that paracetamol, doxorubicin and simvastatine cause hepatic damage and gastroenteropathy (GPT values and the gastric lesions are % higher compared both with the corresponding groups treated with the drug, in the absence of L-NAME, and with the controls treated with L-NAME).

These drugs can therefore be used for preparing the products of the invention.

Omeprazol and misoprostol should not instead be used, on the basis of this test, for preparing the products of the invention.

EXAMPLE F4

Test 4: inhibition of the radical production from DPPH of some substances used as precursors of B or B1 (ref. Formulas I and II of the invention)

The method is based on a colorimetric test in which DPPH (2,2-diphenyl-1-picryl-hydrazyl) is used as the compound-forming radicals (M.S. Nenseter et Al., Atheroscler. Thromb. 15, 1338-1344, 1995).

Solutions in methanol of the tested substances at a final concentration 100 μ M are initially prepared. 0.1 ml of each of these solutions are added to aliquots of 1 ml of a methanol solution 0.1 M of DPPH and then the final volume is brought to 1.5 ml. After having stored the solutions at room temperature away from light for 30 minutes, the absorbance at the wave length of 517 nm is read. It is determined the absorbance decrease with respect to the absorbance of a solution containing the same concentration of DPPH.

The efficacy of the test compound to inhibit the production of radicals, or antiradical activity, is expressed by the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are, respectively, the absorbance values of the solution containing the test compound together + DPPH and of the solution containing only DPPH.

The compound to be used according to the present invention does not meet test 4 if it inhibits radical production as abo-

ve defined by a percentage of 50% or higher.

In Table V the results obtained with the following substances are reported: N-acetylcysteine, cysteine, ferulic acid, (L)-carnosine, gentisic acid, 4-thiazolidin carboxylic acid and 2-oxo-4-thiazolidin carboxylic acid.

Table V shows that:

- N-acetylcysteine, cysteine, ferulic acid, (L)-carnosine, gentisic acid meet test 4 since they inhibit the production of radicals induced by DPPH in an extent higher than 50%, therefore they cannot be used as precursors of B or B₁ of the compounds of the invention.
- 4-Thiazolidin carboxylic acid and 2-oxo-4-thiazolidin carboxylic acid do not meet test 4 since they do not inhibit radical production from DPPH in an extent equal or higher than 50%, and therefore they can be used as precursors of compounds B or B₁ according to the present invention, provided they meet following test 5.

EXAMPLE F5

Test 5: inhibition of the radical production from Fe^{II} from compounds used as precursors of B, B₁ or C = -T_C-Y-H

0.1 ml aliquots of 10⁻⁴ M methanolic solutions of 4-thiazolidin carboxylic acid and 2-oxo-4-thiazolidin carboxylic acid are added to test tubes containing an aqueous solution formed by mixing 0.2 ml of 2 mM deoxyribose, 0.4 ml of buffer phosphate pH 7.4 100 mM and 0.1 ml of 1 mM Fe^{II}(NH₄)₂(SO₄)₂ in

2mM HCl. The test tubes are then kept at a temperature of 37°C for one hour. Then in each test tube are added in the order 0.5 ml of a 2.8% solution in trichloroacetic acid in water and 0.5 ml of an aqueous solution 0.1 M thio barbituric acid. A reference blank is constituted by substituting the above 0.1 ml aliquots of the test compound methanolic solutions with 0.1 ml of methanol. The test tubes are closed and heated in an oil bath at 100°C for 15 minutes. A pink coloration develops the intensity of which is proportional to the quantity of deoxyribose undergone to radical oxidative degradation. The solutions are cooled at room temperature and their absorbances at 532 nm are read against the blank.

The inhibition induced by the precursor of B or B₁ or C = -T_C-Y-H (wherein the free valence is saturated as above defined) in the confront of radical production from Fe^{II} is determined as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound + the iron salt and that of the solution containing only the iron salt. The results are reported in Table III, from which it is drawn that both acids meet test 5, since they inhibit radical production from Fe^{II} in a percentage higher than 50%. Therefore both 4-thiazolidin carboxylic acid and 2-oxo-4-thiazolidin carboxylic acid can be used as precursors of B, B₁ or of C = -T_C-Y-H, for

obtaining the compounds of the present invention.

EXAMPLE F6

Gastric tolerability test of the compounds according to the invention in the confront of the corresponding precursor drugs in conditions of endothelial dysfunctions induced by L-NAME (N^w-nitro-L-arginine-methyl ester).

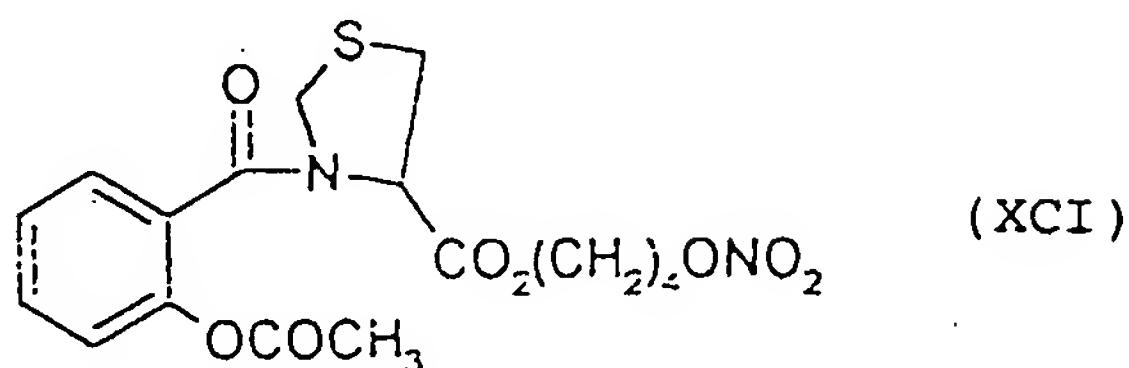
Example F3 was repeated and it was evaluated the gastric tolerability both of the following precursor drugs and of the corresponding derivatives according to the present invention:

- Diclofenac and the corresponding derivative according to Ex. 4.
- Ambroxol and the corresponding derivative according to Ex. 7.
- Alendronate and the corresponding derivative according to Ex. 6.
- Tacrine and corresponding derivative according to Ex. 5.

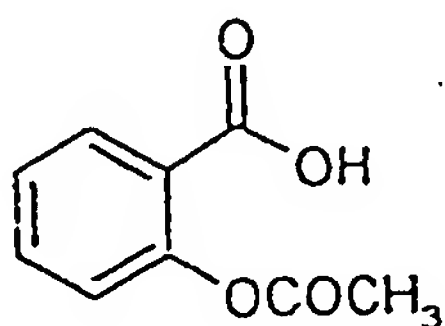
The results are reported in Table VI and show that, by administering at the same dose the compounds of the invention and the corresponding precursor drug, gastropathy incidence results remarkably reduced or disappeared in the groups treated with the compounds of the invention.

EXAMPLE 8

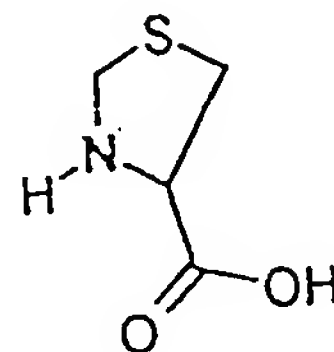
Synthesis of 3-[2-(acetyloxy)benzoyl]thiazolidin-4-carboxylic acid-4-(nitroxy)butyl ester (formula XCI).



starting from acetylsalicylic acid (XCII) and thiazolidin-4-carboxylic acid (formula PIV)



(XCII)



(PIV)

Compound (XCI) is synthesized according to the scheme given in Example 3. Yield : 26%.

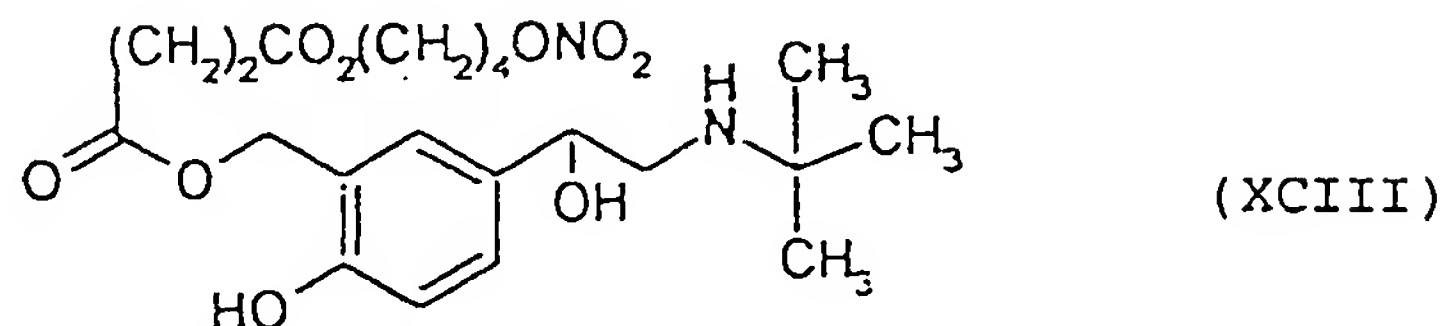
Elemental analysis

calculated %	C 49.51	H 4.89	N 6.79	S 7.77
found%	C 49.57	H 4.94	N 6.70	S 7.73

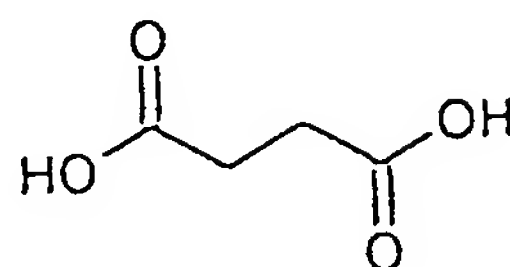
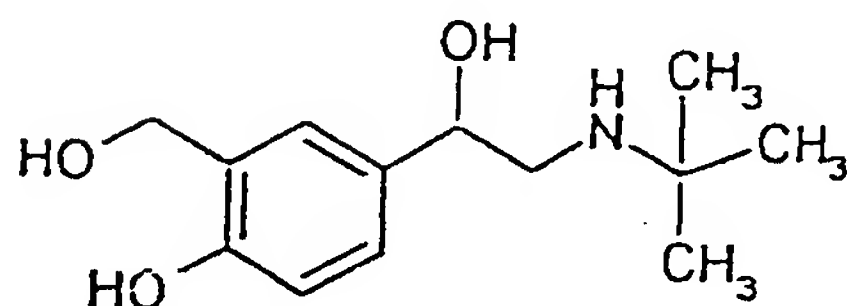
EXAMPLE 9

Synthesis of 2-(tert-butylamino)-1-[4-hydroxy-3[4-oxo-(4-

nitroxybutyloxy)butyryloxy]methylphenyl]ethanol of formula (XCIII)



starting from salbutamol (XXV) and succinic acid (formula RI).



Compound (XCIII) is obtained according to the procedure followed in Example 7. Yield : 14%.

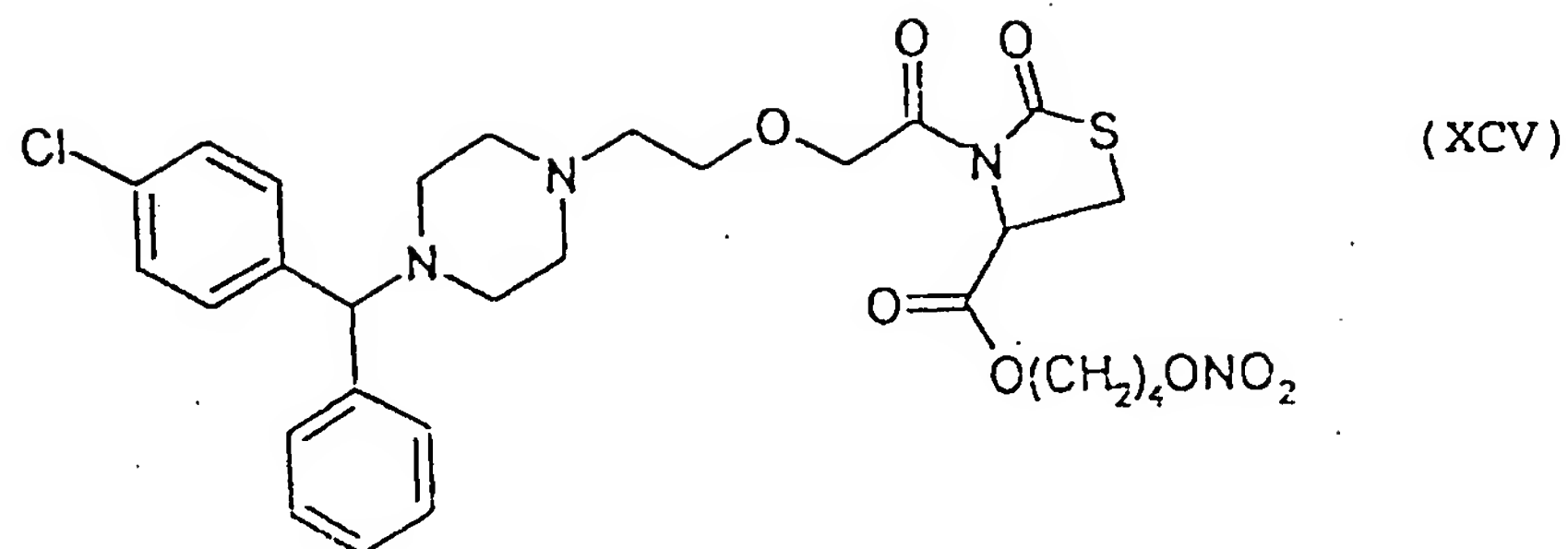
Elemental analysis

calculated % C 55.26 H 7.06 N 6.14

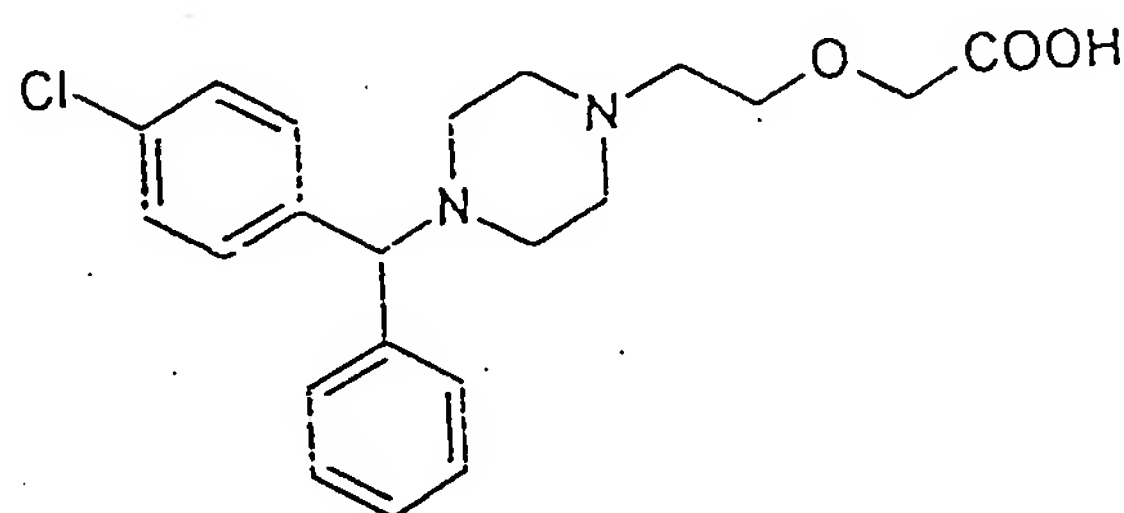
found% C 55.20 H 7.10 N 6.17

EXAMPLE 10

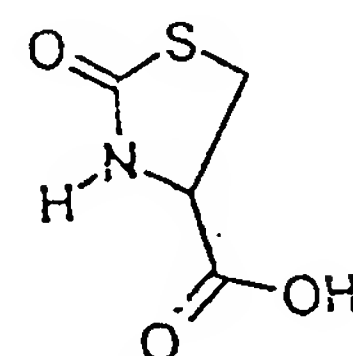
Synthesis of 3-[[2-[4-[(4-chlorophenyl)phenylmethyl]-1-pyperazinyl]ethoxy]acetyl]-thiazolidin-4-carboxylic acid-4-(nitroxy)butyl ester of formula (XCV)



starting from cetirizine (XIV) and 2-oxo-4-thiazolidin carboxylic acid (formula PV)



(XIV)



(PV)

Compound (XCVIII) is obtained according to the procedure followed in Example 3. Yield : 18%.

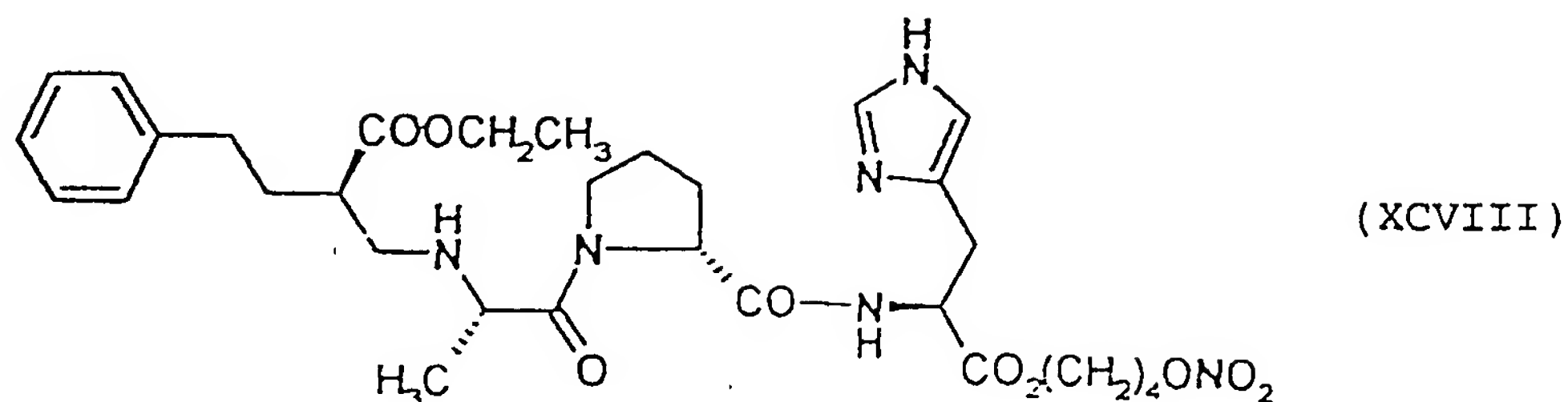
Elemental analysis

calculated % C 55.44 H 5.63 N 7.66 Cl 5.65

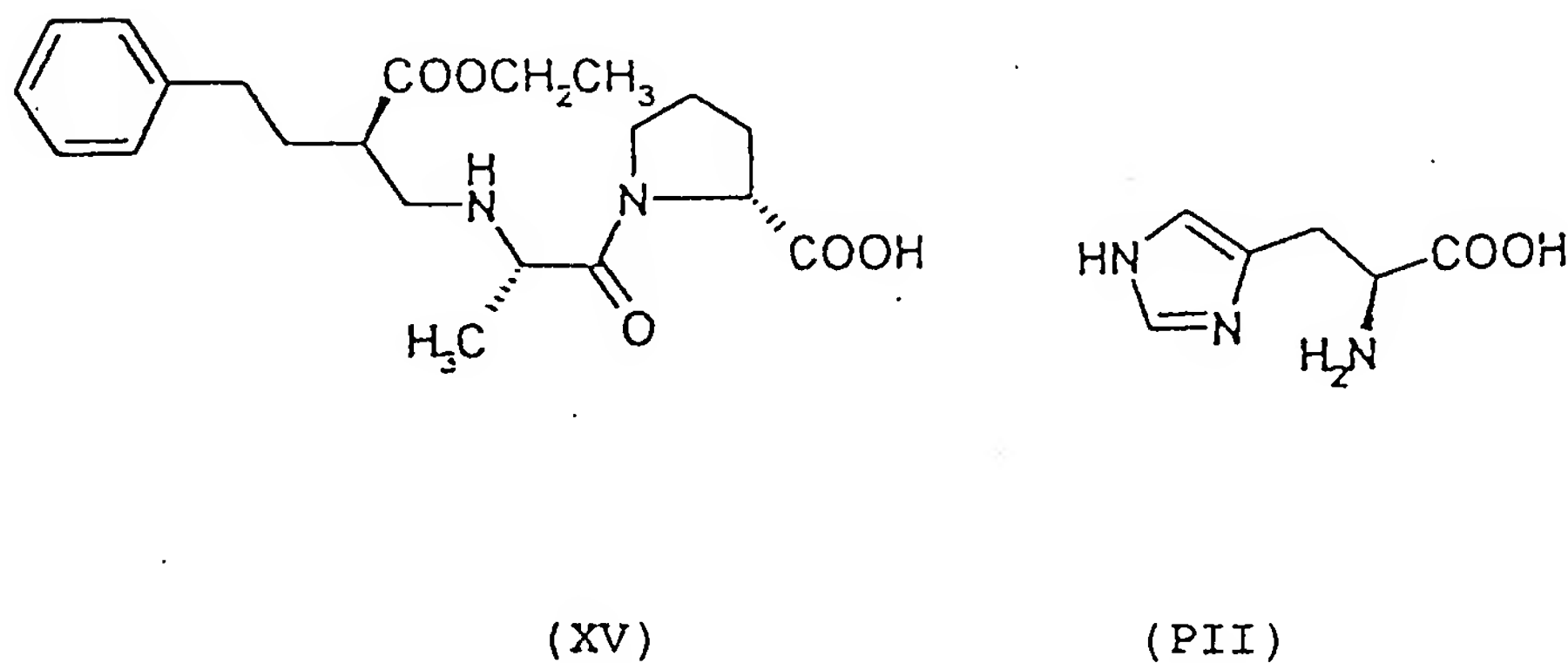
found% C 55.48 H 5.60 N 7.61 Cl 6.71

EXAMPLE 11

Synthesis of N[(S)-1-[N[1-(ethoxycarbonyl)-3-phenylpropyl]-L-Alanyl]-L-prolinyl] histidine 4(nitroxy)butyl ester of formula (XCVIII)



starting from enalapril of formula (XV) and histidine of formula (PII):



Compound (XCVIII) is obtained according to the procedure of Example 7. Yield : 14%.

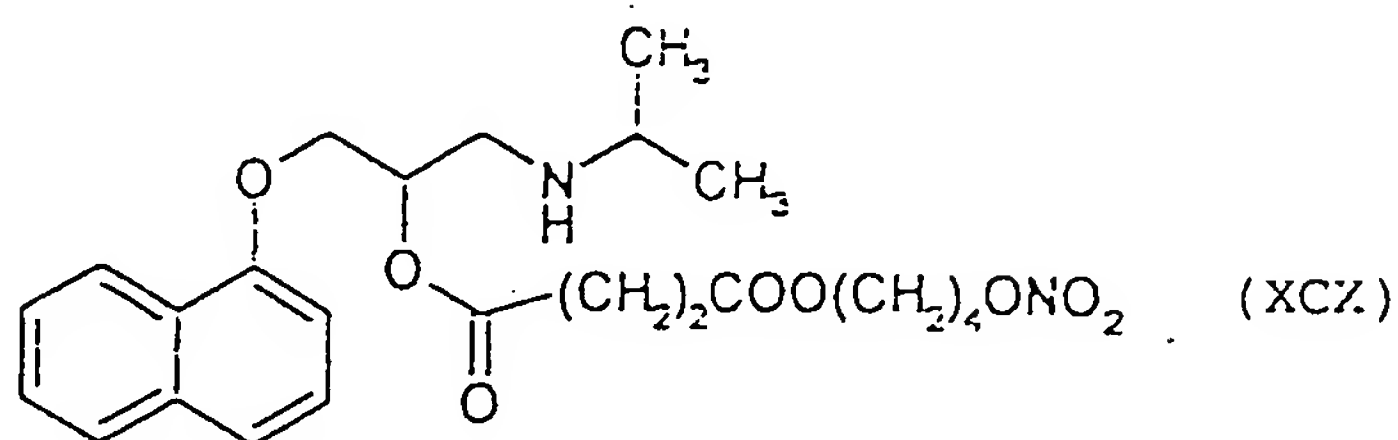
Elemental analysis

calculated % C 57.75 H 6.88 N 13.04

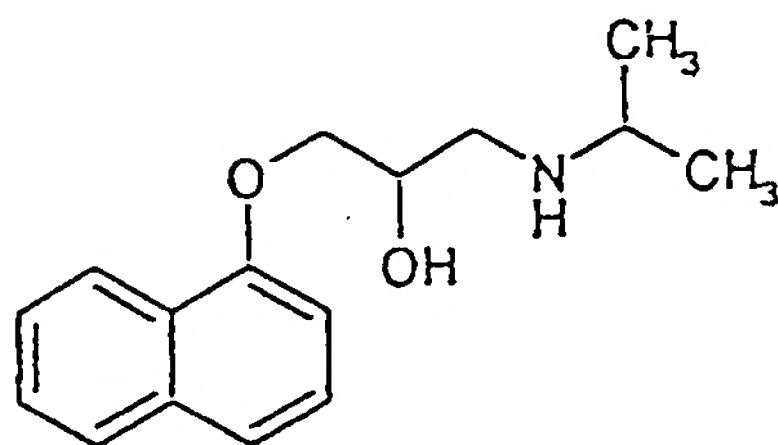
found% C 57.85 H 6.95 N 13.01

EXAMPLE 12

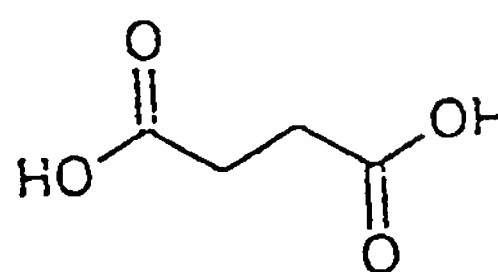
Synthesis of 1-[(1-methylethyl)amino]-3-(1-naphtalenoxy)-2-[4-oxo-(4-nitroxybutyloxy)butanoyl]oxy propane of formula (XCX)



starting from propranolol of formula (XXIV) and succinic acid of formula (RI):



(XXIV)



(RI)

Compound (XCX) is obtained according to the procedure of Example 7. Yield : 30%.

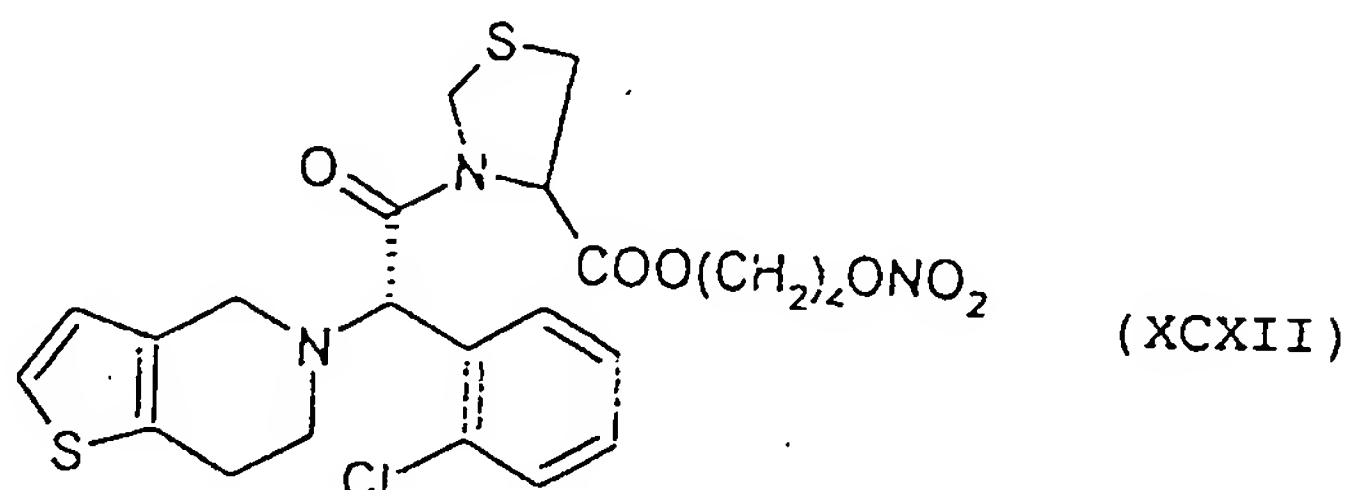
Elemental analysis

calculated % C 60.49 H 6.77 N 5.88

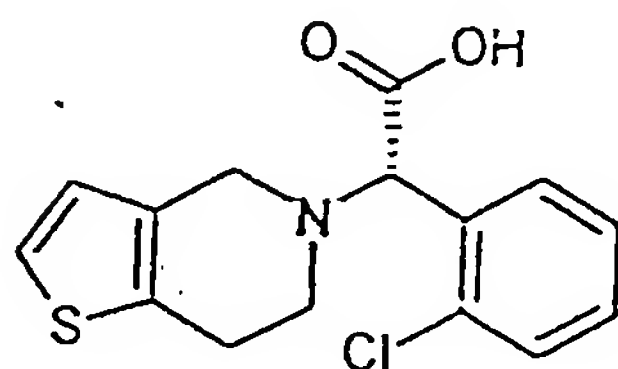
found% C 60.40 H 6.75 N 5.91

EXAMPLE 13

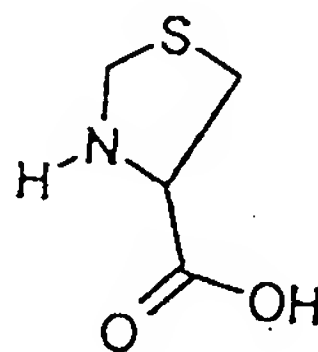
Synthesis of 3-[α -(2-chlorophenyl)-6,7-dihydro-thienol[3.2-c]pyridine-5(4H)acetyl]thiazolidin-4-carboxylic acid 4-(nitroxy)butyl ester of formula (XCXII)



starting from clopidogrel of formula (XI) and thiazolidin-4-carboxylic acid of formula (PIV):



(XI)



(PIV)

Compound (XCXII) is obtained according to the procedure followed in Example 1. Yield : 15%.

Elemental analysis

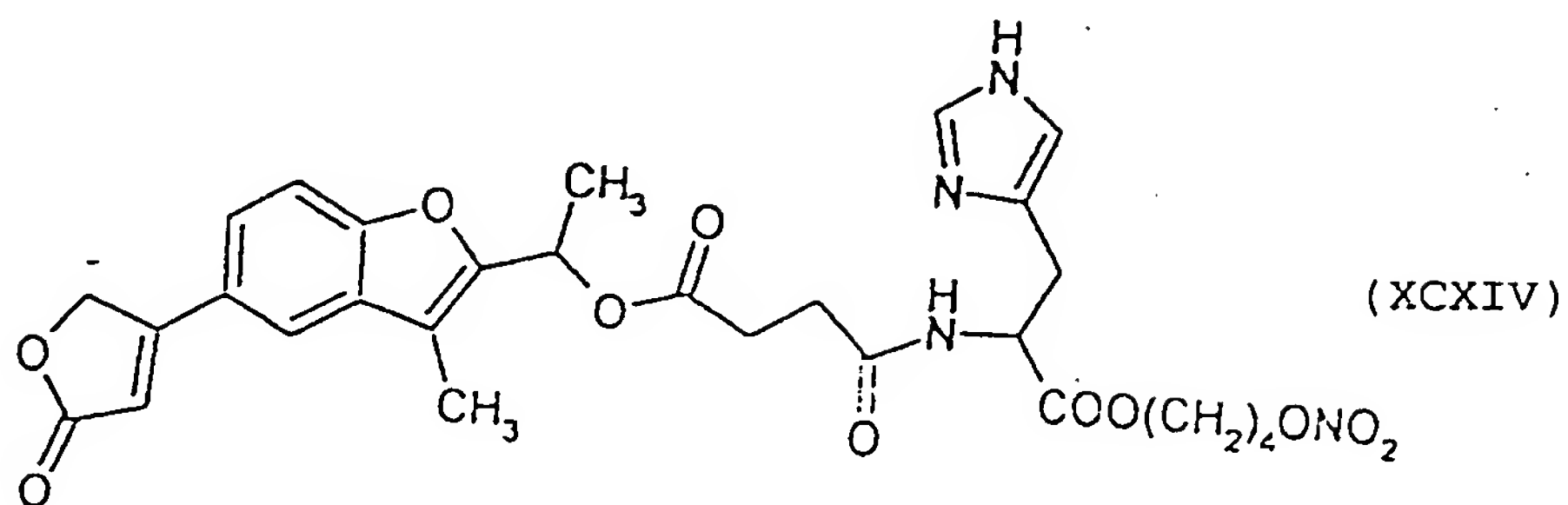
calculated % C 51.15 H 4.85 N 7.78 S 11.87 Cl 6.56

found% C 55.48 H 5.60 N 7.61 S 11.85 Cl 6.59

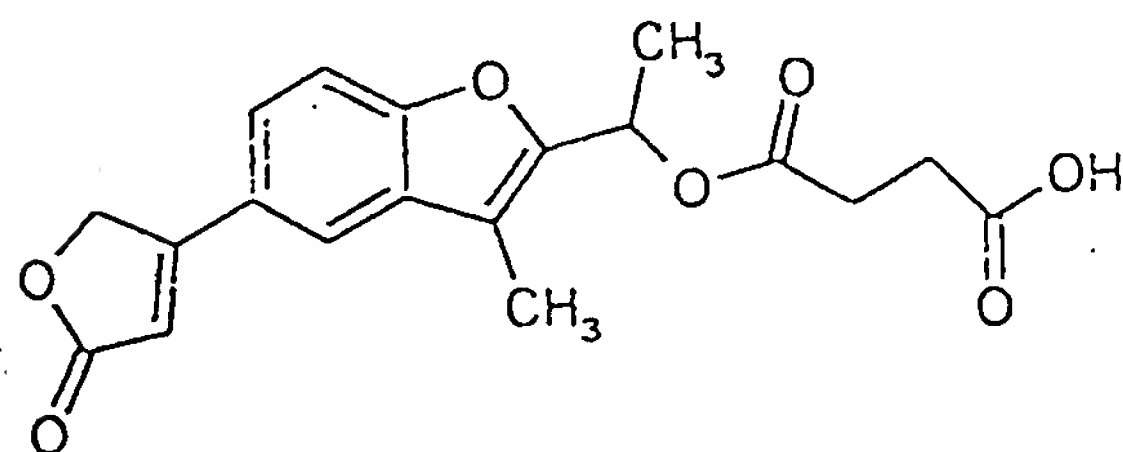
EXAMPLE 14

Synthesis of α N-[1-[5-(2,5-dihydro-5-oxo-3-furanyl)-3-methyl-2-benzofuranyl]ethyloxy-4-oxo-butanoyl] hystidine 4(nitroxy)butyl

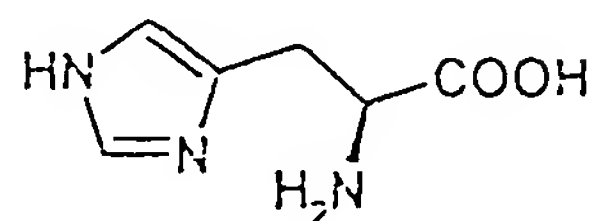
ester of formula (XCXIV)



starting from benfurodil hemisuccinate of formula (XXXI) and
 hystidine of formula (PII)



(XXXI)



(PII)

Compound (XCXIV) was obtained following the procedure described
 in Example 4. Yield : 35%.

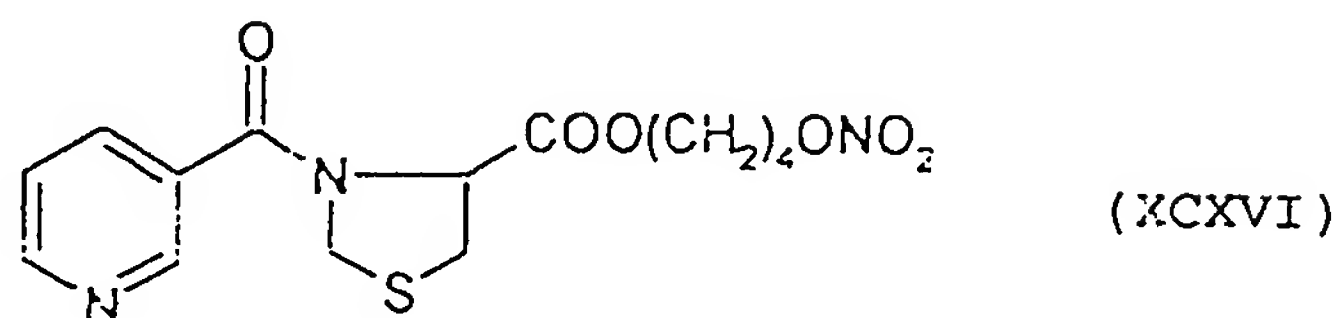
Elemental analysis

calculated % C 56.86 H 5.26 N 9.15

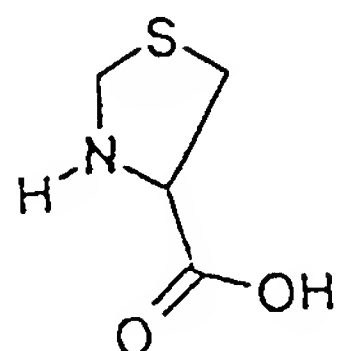
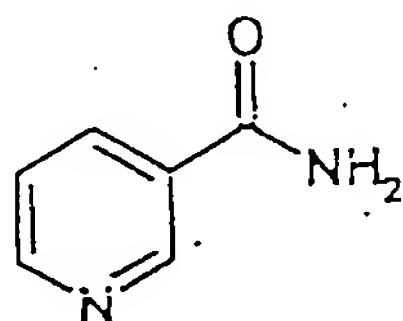
found% C 56.92 H 5.29 N 9.10

EXAMPLE 15

Synthesis of 3-nicotinoyl-thiazolidin carboxylic acid (4-nitroxy)butyl ester of formula (XCXVI)



starting from nicotinamide of formula (XXIII) and thiazolidin-4-carboxylic acid of formula (PIV)



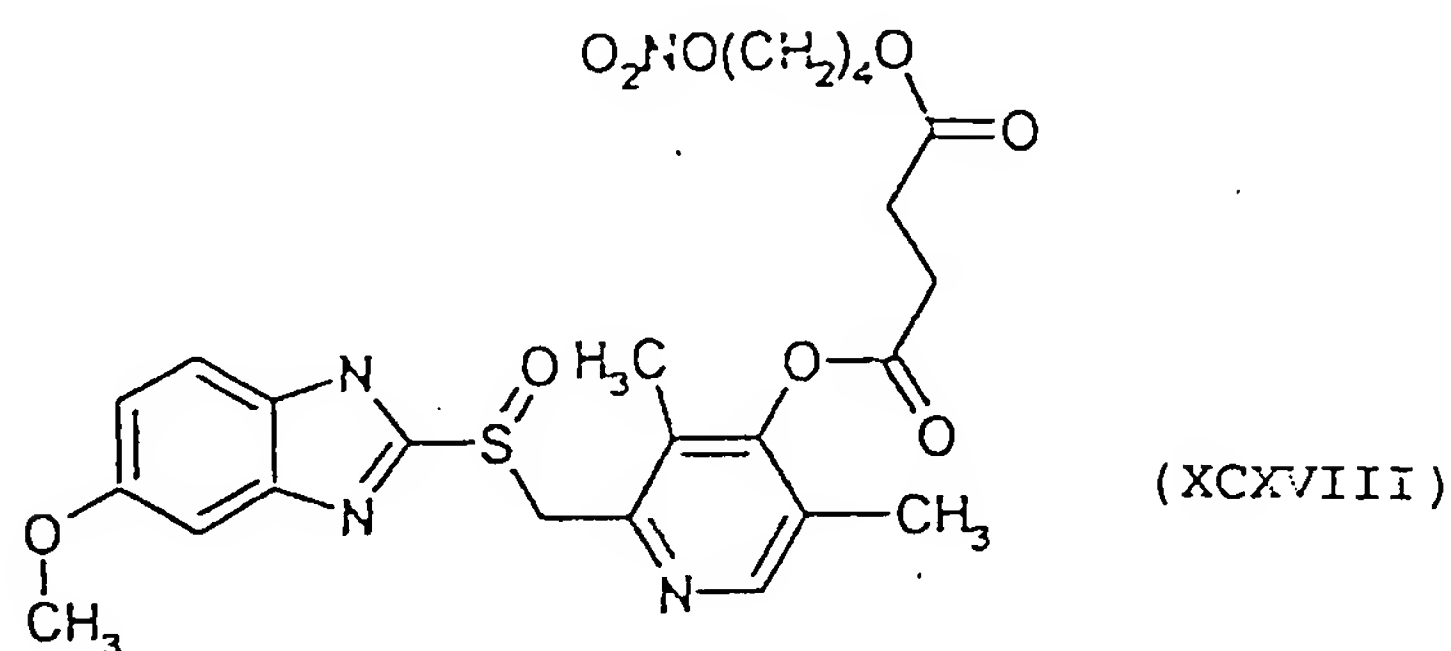
Compound (XXIII) was synthesized according to the procedure described in Example 1, using nicotinic acid. Yield 35%.

Elemental analysis

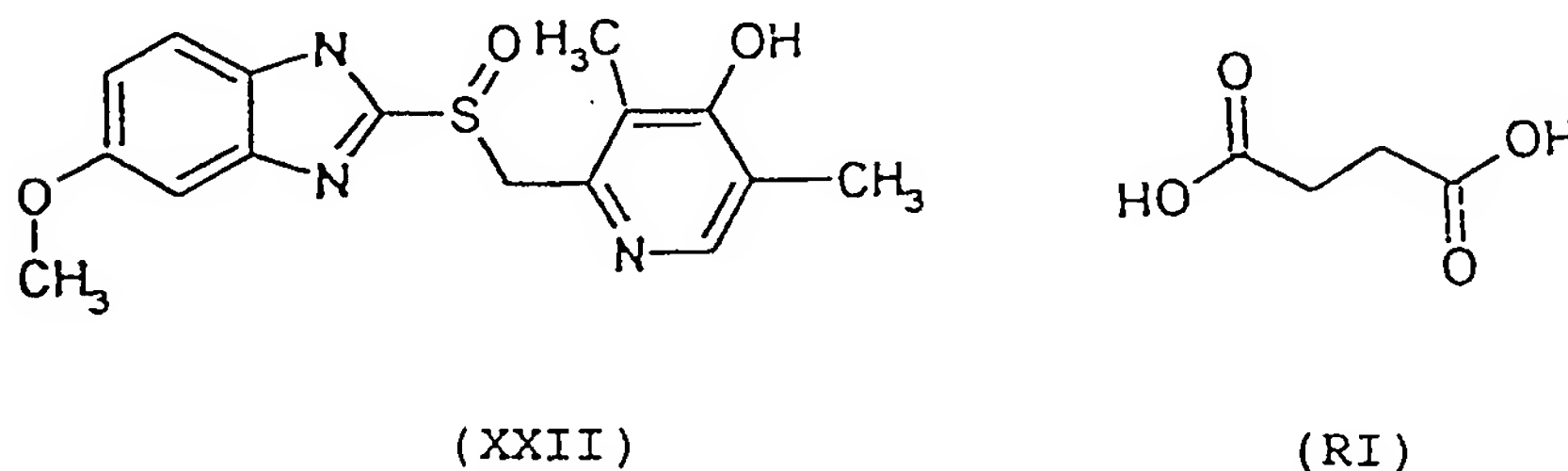
calculated %	C 47.32	H 4.82	N 11.82	S 9.01
found%	C 47.30	H 4.79	N 11.84	S 9.06

EXAMPLE 16

Synthesis of 5-methoxy-2-[[[4-oxo-4-(nitroxy)butyryloxy]-3,5-dimethyl-2-pyridinyl]methyl]sulphonyl]-1H-benzimidazole of formula (XCXVIII)



starting from 4-hydroxyomeprazole of formula (XXII) and succinic acid of formula (RI)



Compound (XCXVIII) was obtained following the procedure described in Example 7. Yield 15%

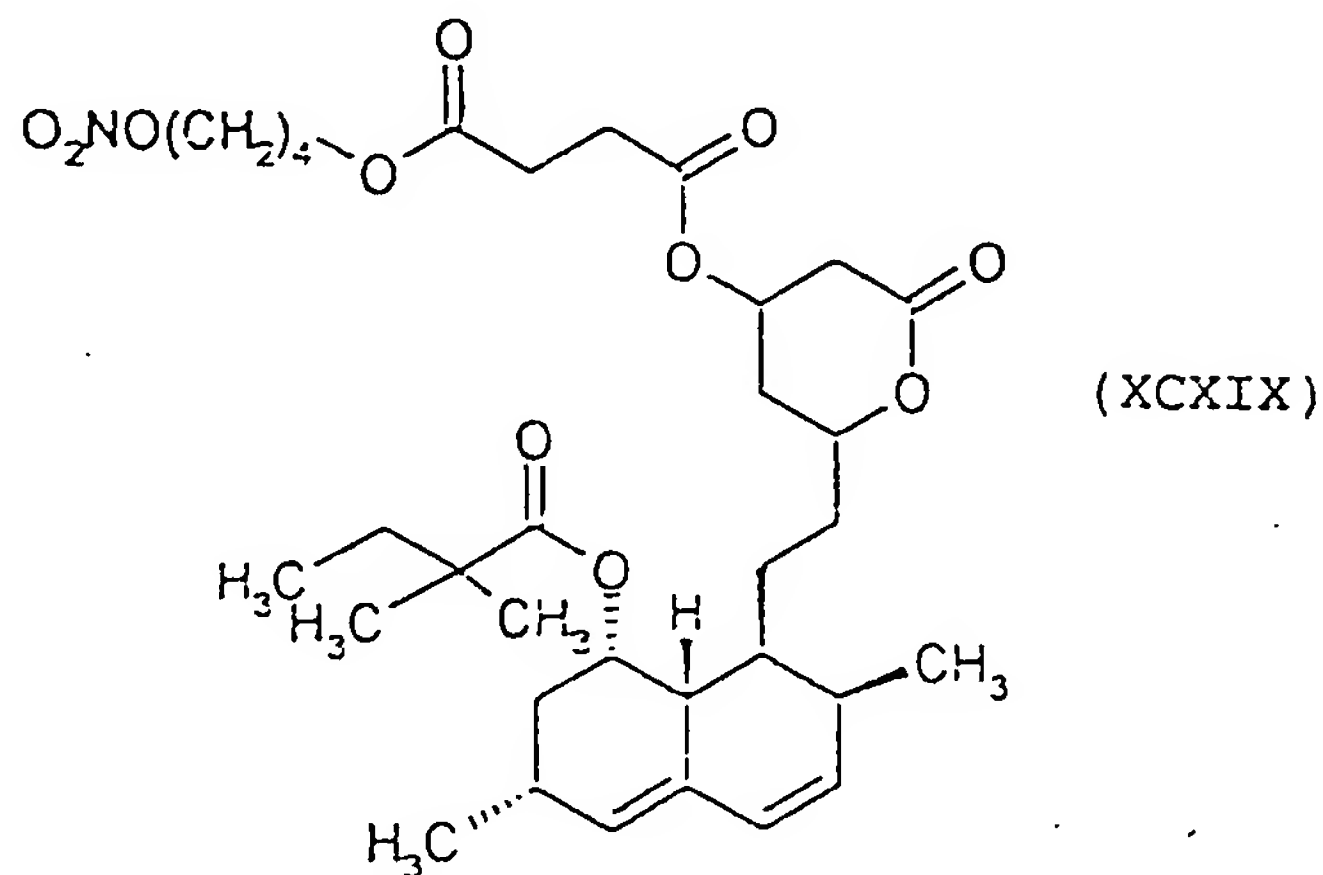
Elemental analysis

calculated %	C 52.64	H 4.97	N 10.23	S 5.86
found%	C 52.68	H 5.01	N 10.15	S 5.81

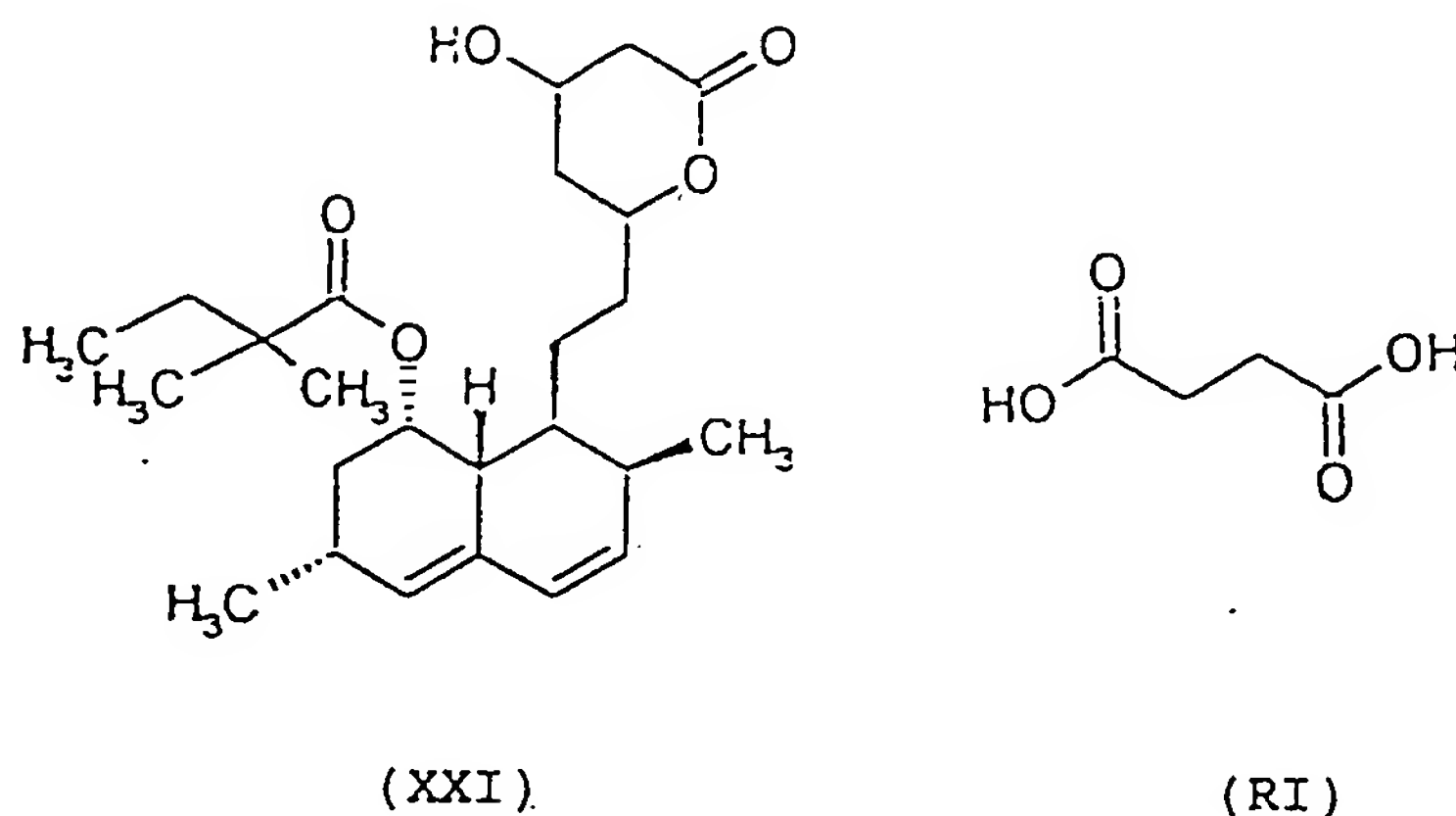
EXAMPLE 17

Synthesis of [1S-[1 α ,3 α ,7 β ,8 β , (2S*,4S*)]]-2,2-dimethylbutanoic

acid 1,2,3,7,8,8-hexahydro-3,7-dimethyl-8-[2-[tetrahydro-4-[4-oxo-(4-nitroxybutyloxy)butyryloxy]-6-oxo-2H-piran-2-yl]ethyl]-1-naphthalenyl ester of formula (XCXIX)



starting from simvastatine of formula (XXI) and succinic acid of formula (RI)



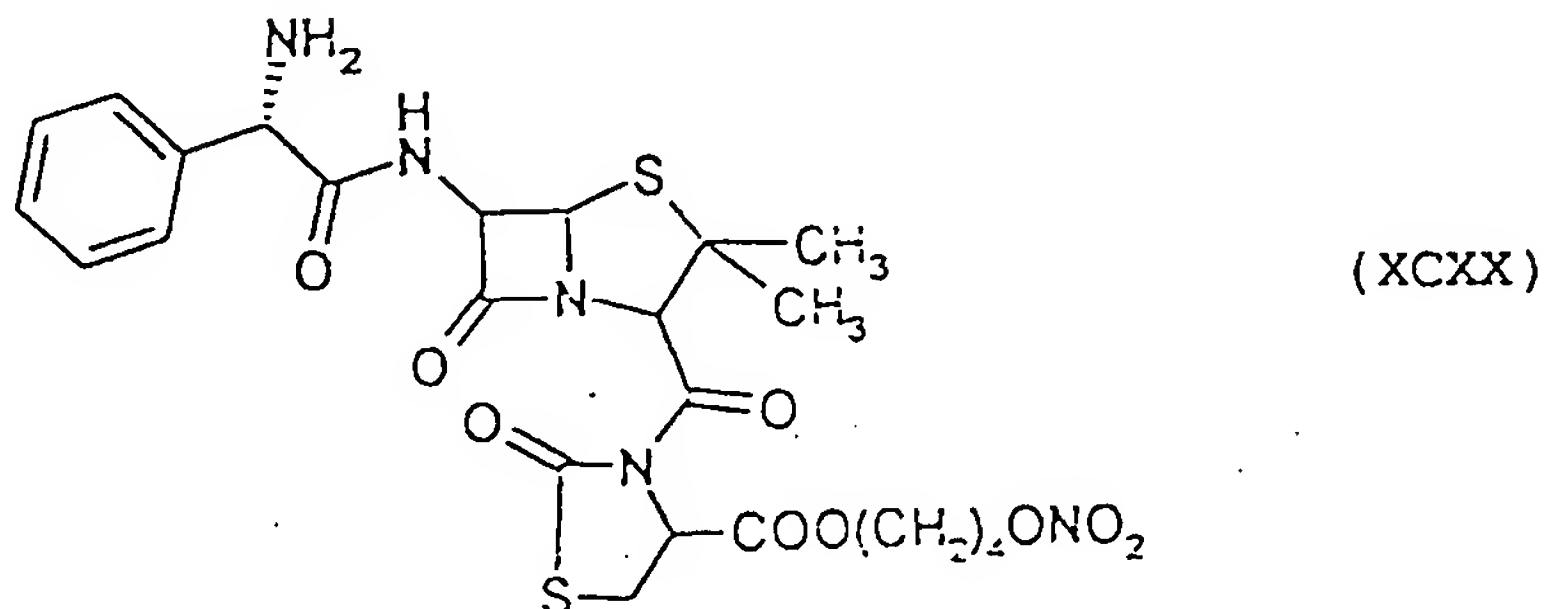
Compound (XCXIX) was synthesized following the procedure of Example 7. Yield 12%.

Elemental analysis

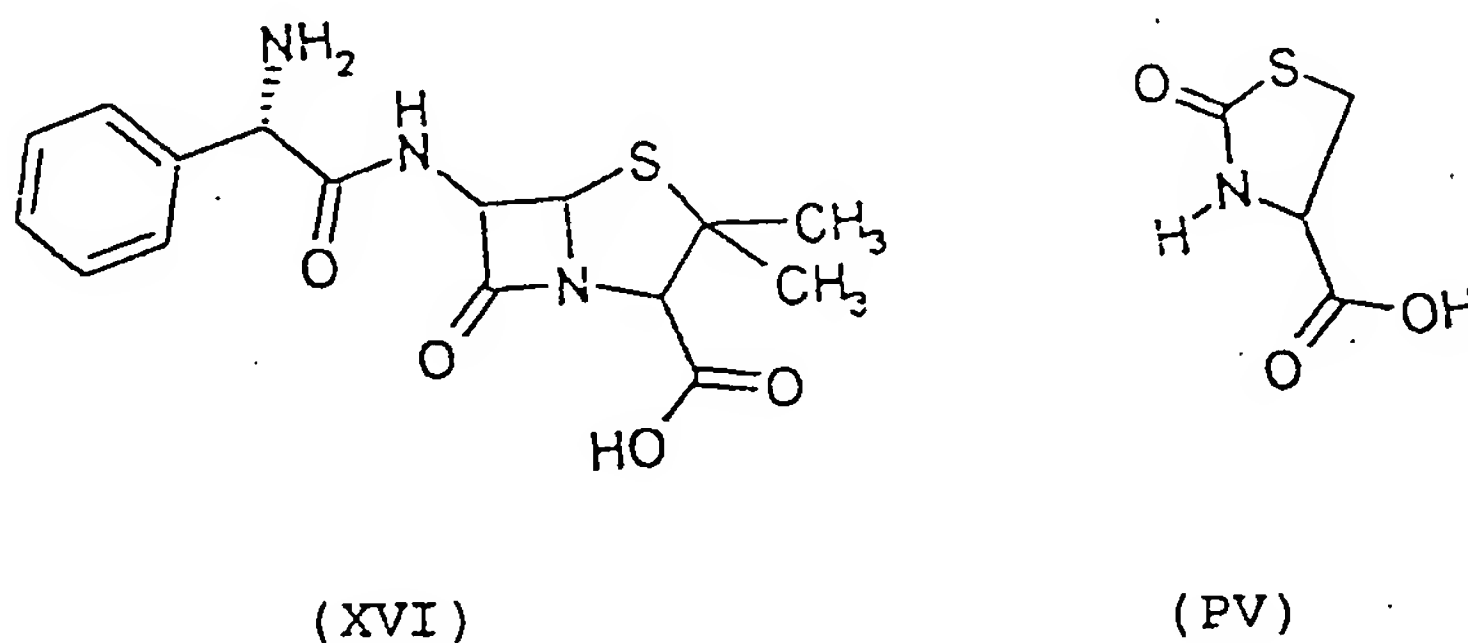
calculated %	C 62.35	H 7.77	N 2.20
found%	C 62.50	H 7.81	N 2.17

EXAMPLE 18

Synthesis of 3-[4-D- α -aminobenzylpenicillaminoyl]thiazolidin carboxylic acid 4-(nitroxy)butyl ester of formula (XCXX)



starting from ampicillin of formula (XVI) and 2-oxo-4-thiazolidin carboxylic acid of formula (PV)



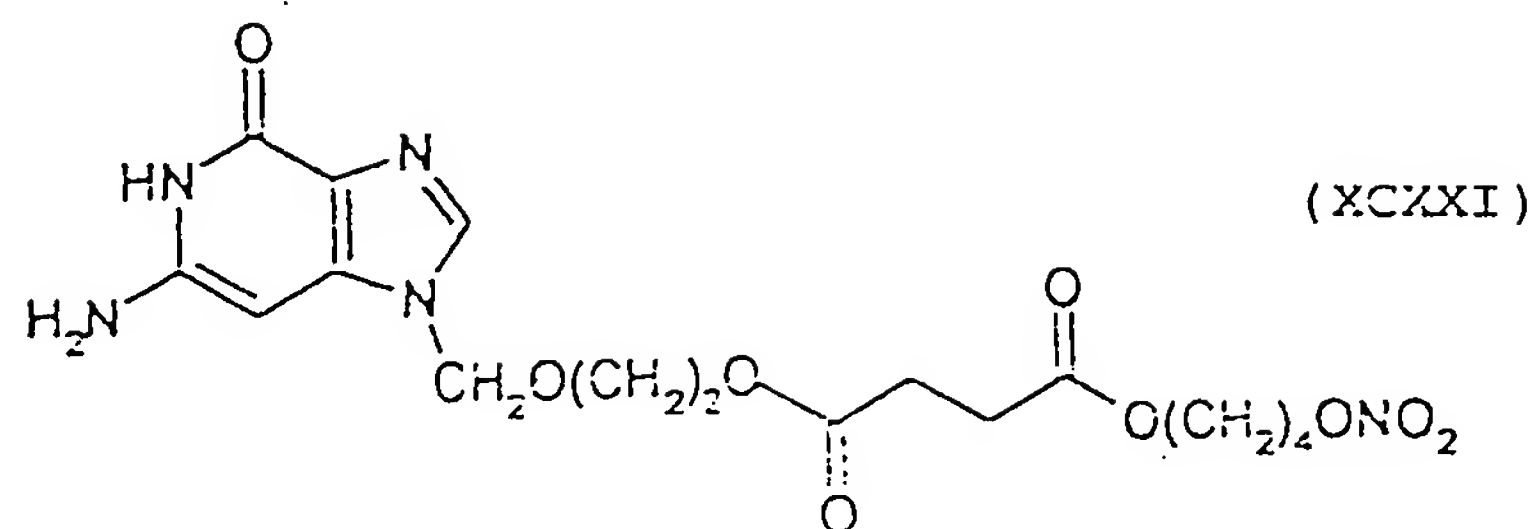
Compound (XCXX) was obtained following the procedure of Example 3. Yield 19%.

Elemental analysis

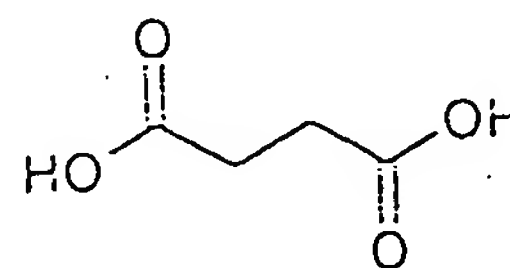
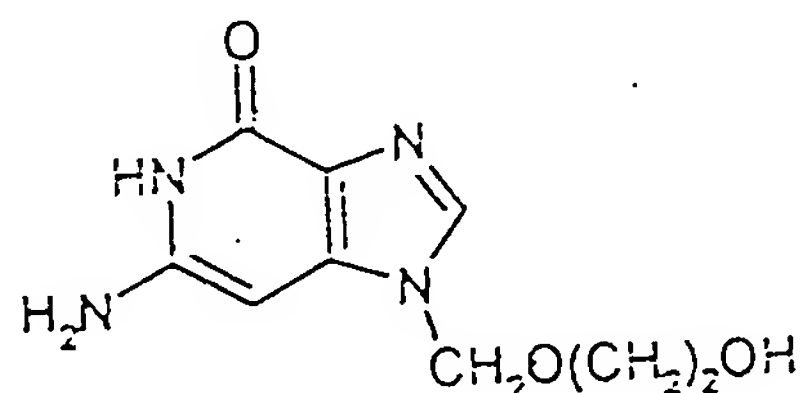
calculated %	C 48.39	H 4.91	N 11.76	S 10.77
found%	C 48.43	H 4.99	N 11.71	S 10.74

EXAMPLE 19

Synthesis of 9-[[2-[4-oxo-(4-nitroxybutyloxy)butyryloxy]ethoxy]-methyl]guanine of formula (XCXXI)



starting from acyclovir of formula (XVII) and succinic acid of formula (RI)



Compound (XCXXI) was synthesized following the procedure of Example 7. Yield : 23%.

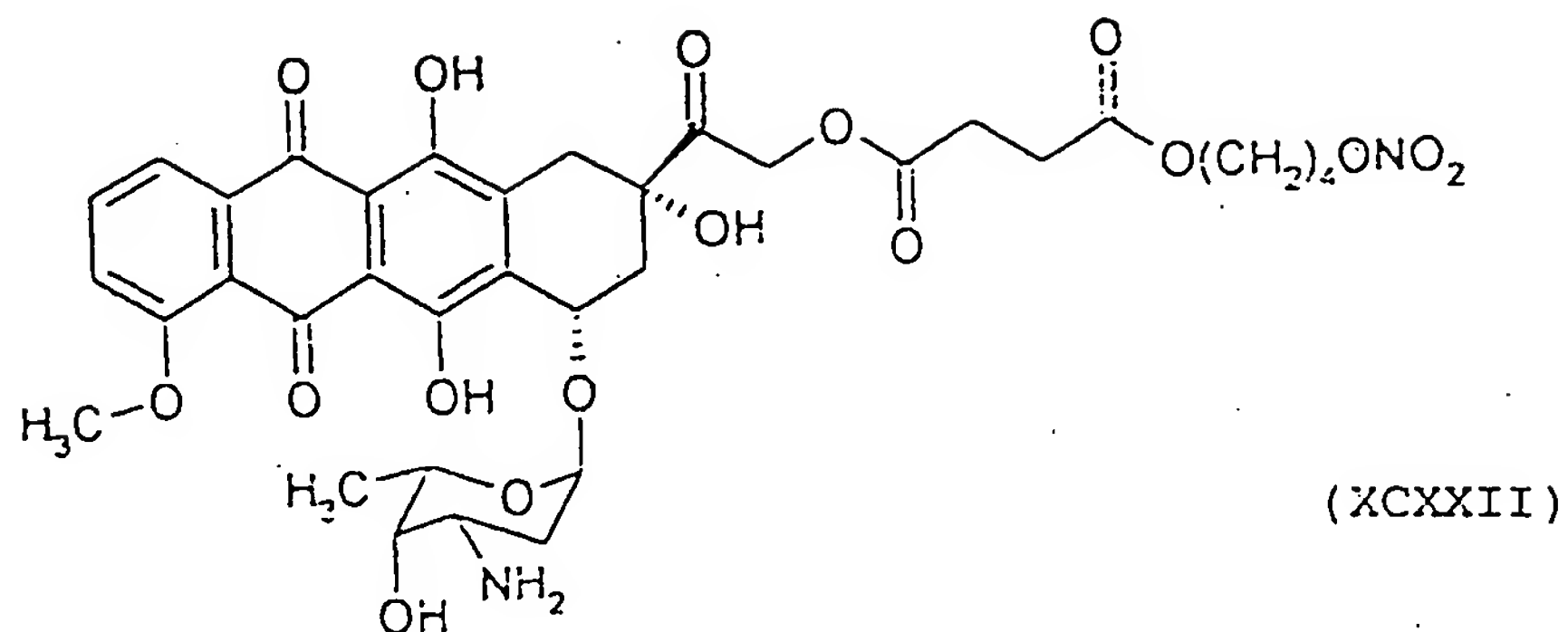
Elemental analysis

calculated % C 46.26 H 5.25 N 15.85

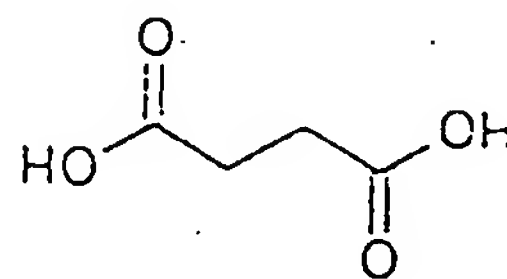
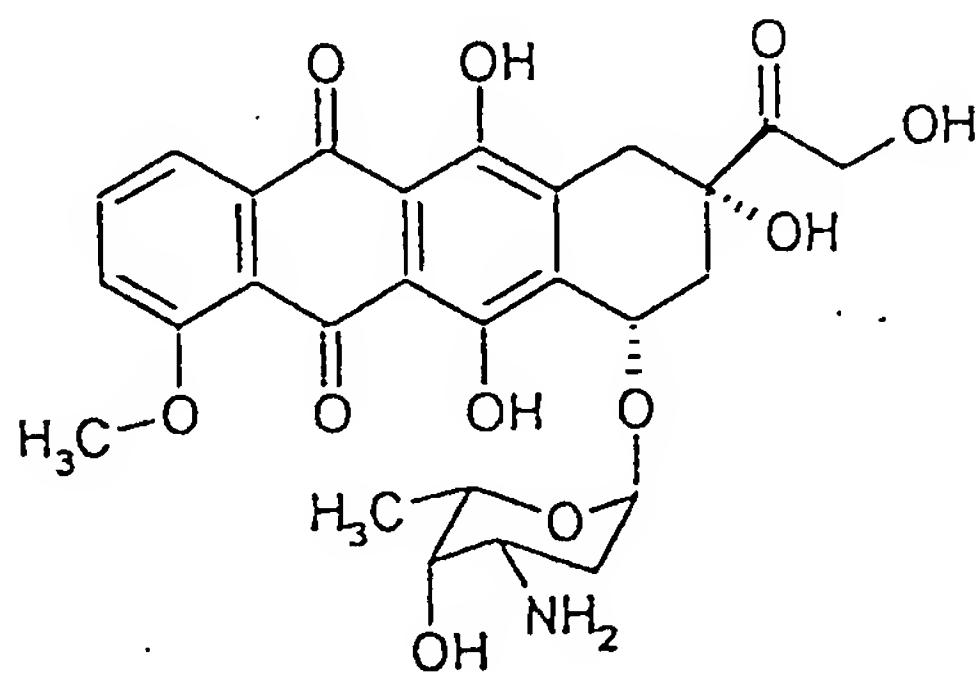
found% C 46.30 H 5.28 N 15.84

EXAMPLE 20

Synthesis of (8S-cis)-10[(3-amino,2,3,6-tri-deoxy- α -L-lyxo-exo pyranosyl)oxy]-7,8,9,10-tetrahydro,6,8,11-trihydroxy-8-[[[4-oxo-(4-nitroxybutyloxy)butiryl-oxy-]methyl-oxo]-1-methoxy-5,12-naphtacenedione of formula (XCXXII)



starting from doxorubicin of formula (XXXII) and succinic acid of formula (RI)



Compound (XCXXII) was synthesized according to the procedure of Example 7. Yield 10%.

Elemental analysis

calculated %	C 55.26	H 5.30	N 3.68
found%	C 55.34	H 5.32	N 3.65

EXAMPLE F7

Example F1 was repeated with four groups of rats (each group of ten animals), all of them receiving NEM, and orally administered as it follows :

- a. control group : the vehicle formed of an aqueous suspension 1% w/v of carboxymethylcellulose,
- b. one group (group b - comparative) administered at the same time with 5 mg/Kg (0.02 mmoles/Kg) of flurbiprofen + 2.7 mg/Kg (0.02 mmoles/Kg) of 4-thiazolidin carboxylic acid in the same above vehicle,
- c. one group (group c - comparative) administered at the same time with 7.4 mg/Kg (0.02 mmoles/Kg) of 4-(nitroxy)butyl ester of flurbiprofen, synthetized according to the method described in WO 94/12463, + 2.7 mg/Kg (0.02 mmoles/Kg) of 4-thiazolidin carboxylic in the same above vehicle,
- d. one group (group d) administered with 9.8 mg/Kg (0.02 mmoles/Kg) of 3-[2-fluoro- α -methyl-(1,1'-biphenyl)-4-acetyl]thiazolidin-4-carboxylic acid 4-(nitroxy)butyl ester synthetized as from Ex. 1 (indicated as NO-Flurbiprofen in Table VII), in the above same vehicle.

The results are reported in Table VII and show that the mixtures administered respectively to groups b and c (comparatives), differently from the compound of the invention administered to group d, were almost ineffective (group b) or much less effective (group c) in reducing gastric lesions.

Table I

Test 1 : Gastric tolerability of drugs representative of the drug classes illustrated in the present invention in animals not treated or treated with NEM (oxidative stress conditions). The % is calculated from the ratio between the number of animals found with gastric lesions and that total of the group.			
Compound	dose (mg/Kg) /admin. route	Gastro-enteropathy (% incidence)	
		without NEM	with NEM
carrier		0	0
Indomethacin	7.5/p.o.	0	100
Ambroxol	25/p.o.	0	80
Mesalamine	750/i.c.	0	60
Alendronate	15/p.o.	0	90
Tacrine	1/s.c.	0	100
Omeprazol	30/s.c.	0	0
Misoprostol	0.5/s.c.	0	0

p.o. = per os; i.c. = by intracolonic route;
s.c. = by subcutaneous route.

Table II

Test 2 : Inhibition of apoptosis (DNA fragmentation) induced by CIP in the endothelial cells in the presence of compounds representative of the drug classes illustrated in the present invention.	
Compound	Apoptosis % with respect to the controls treated only with CIP
Indomethacin	95
Paracetamol	120
Clopidogrel	110
Salbutamol	90
Ambroxol	70
Alendronate	160
Diphylline	95
Cetirizine	115
Enalapril	80
Nicotinamide	98
Ampicilline	94
Aciclovir	95
Mesalamine	74
Tacrine	90
Simvastatine	72
Omeprazol	90

Table III

Test 5 : Screening of the effectiveness of the listed substances to inhibit radical production induced by Fe ^{II}	
Compound	% Radical Inhibition from Fe ^{II}
Blank	0
2-oxo-4-thiazolidin carboxylic acid	100
4-thiazolidin carboxylic acid	100
histidine	90
succinic acid	90

Table IV

Test 3 : Gastric tolerability (gastrointestinal damage incidence), hepatic (GPT, glutamic-pyruvic transaminase dosage), and cardiovascular (blood pressure) of some compounds representative of the drug classes illustrated in the present invention under conditions of endothelial trouble induced by L-NAME. The results relating to the blood pressure and GPT are expressed as % values compared with those found in animals treated with the only carrier, without L-NAME.							
Compound	dose mg/Kg /administ. route	Blood pressure %		GPT %		Gastroenteropathy %	
		without L-NAME	with L-NAME	without L-NAME	with L-NAME	without L-NAME	with L-NAME
Carrier		100	152	100	155	0	30
Paracetamol	300/i.p.	108	155	180	500	20	90
Doxorubicin	1/i.p.	120	145	195	360	30	100
Simvastatine	50/p.o.	85	148	122	220	0	60
Omeprazol	30/s.c.	100	150	100	160	0	10
Misoprostol	0.5/s.c.	100	142	100	160	0	5

Table V

Test 4: Screening of the effectiveness of the listed compounds in inhibiting radical production from DPPH.	
Compound	% inhibition radical production from DPPH
Solvent	0
N-acetylcysteine	100
Cysteine	100
Ferulic acid	100
(L)-carnosine	80
Gentisic acid	80
2-oxo-4-thiazolidin carboxylic acid	0
4-thiazolidin carboxylic acid	0
histidine	0
succinic acid	0

Table VI

Study on gastric tolerability of the listed drugs and of the corresponding derivatives according to the invention on animals not treated or treated with L-NAME				
Compound	animals not treated with L-NAME		animals treated with L-NAME	
	dose mg/Kg	% gastropathy	dose mg/Kg	% gastropathy
Carrier	-	0	-	0
Diclofenac (comp.)	20/p.o.	70	5/p.o.	100
Derivative Ex. 4	20/p.o.	0	5/p.o.	0
Ambroxol (comp.)	100 p.o.	60	25 p.o.	80
Derivative Ex. 7	100 p.o.	10	25 p.o.	0
Alendronate (comp.)	100 p.o.	90	15 p.o.	70
Derivative Ex. 6	100 p.o.	20	15 p.o.	10
Tacrine (comp.)	10/s.c.	80	1/s.c.	70
Derivative Ex. 5	10/s.c.	20	1/s.c.	0

Table VII

Test on gastric tolerability following oral administration of NEM (ex. F7)		
groups	dose mg/Kg p.o.	Gastropathy % incidence
controls	-	-
group b - comparative mixture flurbiprofen (A) + 4-thiazolidin carboxylic acid (B)	5 (A) + 2.7 (B)	80
group c - comparative mixture flurbiprofen 4-(nitroxy)butyl ester (C) + 4-thiazolidin carboxylic acid (B)	7.4 (C) + 2.7 (B)	20
group d NO-Flurbiprofen (ex. 1)	9.8	0

CLAIMS

1. Compounds or their salts having the following general formulas (I) and (II):



wherein:

s = is an integer equal to 1 or 2, preferably s = 2;

bo = 0 or 1;

A = R-T₁-, wherein

R is the drug radical and

T₁ = (CO)_t or (X)_{t'}, wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = -T_B-X₂-T_{BI}- wherein

T_B and T_{BI} are equal or different;

T_B = (CO) when t = 0, T_B = X when t' = 0, X being as above defined;

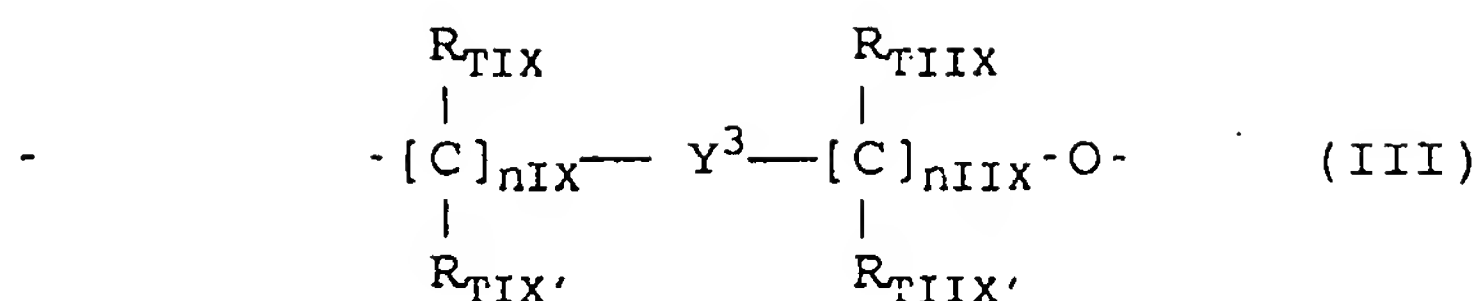
T_{BI} = (CO)_{tx} or (X)_{txx} wherein tx and txx have the 0 or 1 value; with the proviso that tx = 1 when txx = 0, and tx = 0 when txx = 1; X is as above defined;

X₂ is a bivalent bridging bond as defined below;

C is the bivalent -T_C-Y- radical, wherein

T_C = (CO) when tx = 0, T_C = X when txx = 0, X being as above defined;

Y is:



wherein:

nIX is an integer between 0 and 3, preferably 1;

nIIX is an integer between 1 and 3, preferably 1;

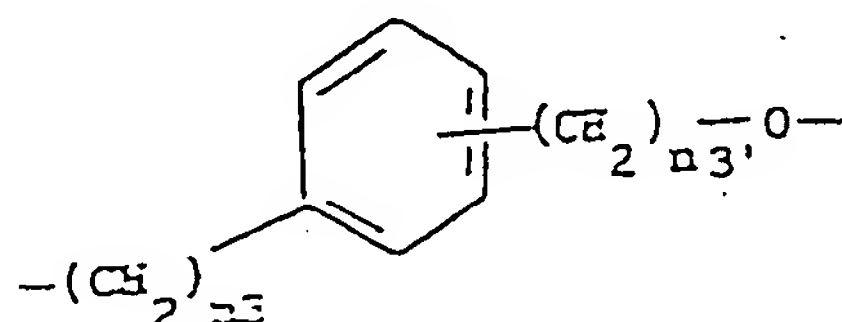
R_{TIX}, R_{TIX'}, R_{TIIIX}, R_{TIIIX'}, equal to or different from

each other are H or a linear or branched C₁-C₄ alkyl; preferably R_{TIX}, R_{TIX'}, R_{TIIIX}, R_{TIIIX'} are H.

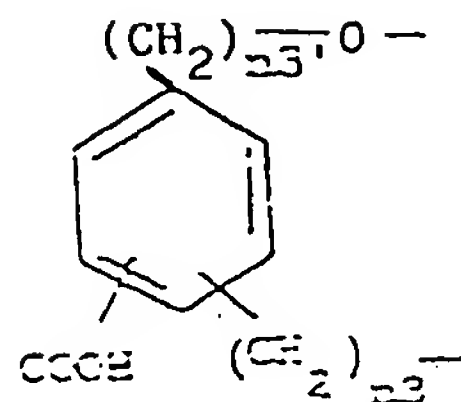
Y³ is a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen atom, said ring having 5 or 6 atoms.

or Y is Y₀, selected from the following:

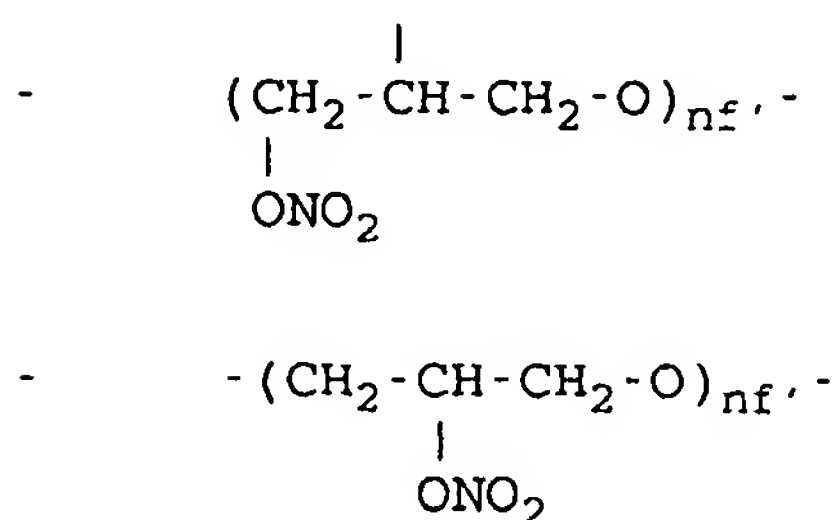
- an alkyleneoxy group R'O wherein R' is linear or when possible branched C₁-C₂₀, preferably having from 1 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylenic ring one or more carbon atoms can be replaced by heteroatoms, the ring can have side chains of R' type, R' being as above defined; or



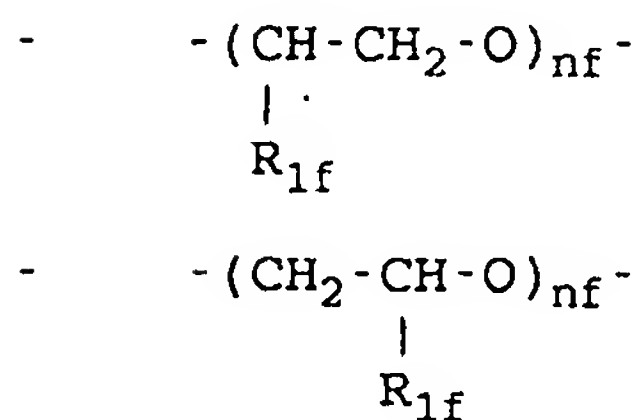
wherein n_3 is an integer from 0 to 3 and n_3' is an integer from 1 to 3;



wherein n_3 and n_3' have the above mentioned meaning



wherein n_f' is an integer from 1 to 6 preferably from 1 to 4;



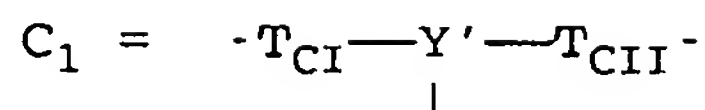
wherein $\text{R}_{1f} = \text{H}, \text{CH}_3$ and n_f is an integer from 1 to 6; preferably from 1 to 4;

preferably $\text{Y} = -\text{R}'\text{O}-$ wherein R' is as above defined;

preferably R' is a C_1 - C_6 alkyl;



wherein:



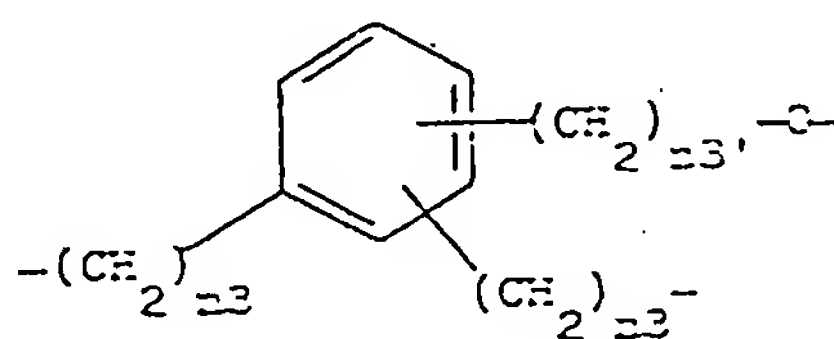
wherein T_{CI} and T_{CII} are equal or different,

$T_{CI} = (CO)$ when $t = 0$, $T_{CI} = X$ when $t' = 0$, X being as above defined;

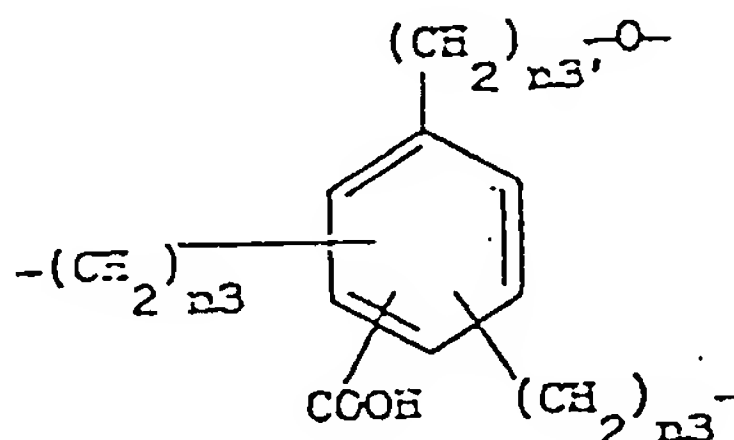
$T_{CII} = (CO)_{tI}$ or $(X)_{tII}$, wherein tI and tII have the 0 or 1 value; with the proviso that $tI = 1$ when $tII = 0$, and $tI = 0$ when $tII = 1$; X is as above defined;

Y' is as Y above defined, but with three free valences instead of two, preferably:

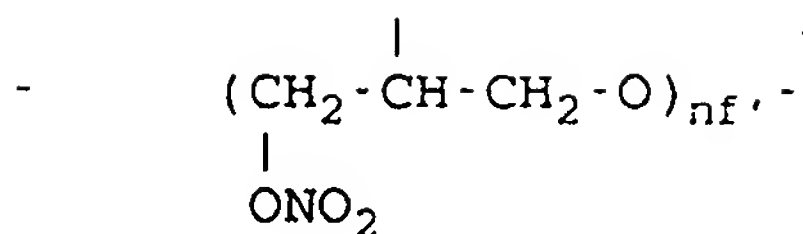
- a $-R'O-$ group wherein R' is as above defined,
|
preferably an alkyl from 2 to 6 carbon atoms,
or



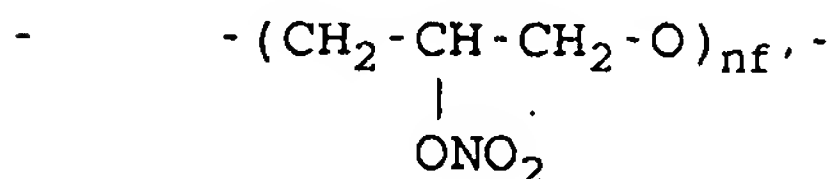
wherein $n3$ is an integer from 0 to 3 and $n3'$ is an integer from 1 to 3;



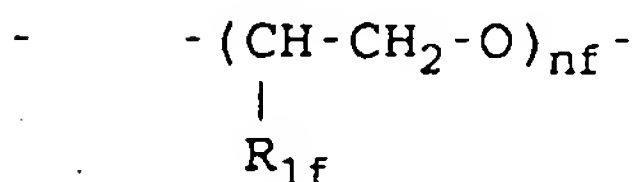
wherein $n3$ and $n3'$ have the above mentioned meaning;



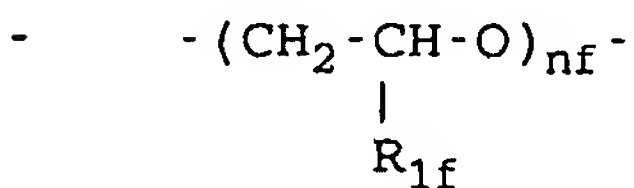
wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein nf' is an integer from 1 to 6 preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein $\text{R}_{1\text{f}} = \text{H}, \text{CH}_3$ and nf is an integer from 1 to 6; preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;

preferably $\text{Y}' = - \text{R}'\text{O}-$ wherein R' is a linear or branched $\text{C}_2 - \text{C}_4$, the oxygen which in Y' is covalently linked to the $-\text{N}(\text{O})_s$ group is at the end of the free bond indicated in the formula

of C_1 ;

$$B_1 = -T_{BII}-X_{2a}$$

wherein X_{2a} is a monovalent radical as defined below,

$T_{BII} = (CO)$ when $tI = 0$, $T_{BII} = X$ when $tII = 0$, X being as above defined;

- X_2 , bivalent radical is such that the corresponding precursor of B: $-T_B-X_2-T_{BI}-$ meets test 5 but not test 4, precursor in which the T_B and T_{BI} free valences are each saturated with $-OZ$, $-Z$, or with $-Z^I-N-Z^{II}$,
 Z^I and Z^{II} being equal or different and have the Z values as defined below, depending on whether T_B and/or $T_{BI} = CO$ or X , in connection with the values of t , t' , tx and txx ;
- the precursor of C when $b0 = 0$ is of $-T_c-Y-H$ type wherein the T_c free valence is saturated with $-OZ$, $-Z$, or with $-Z^I-N-Z^{II}$, Z^I and Z^{II} being as above defined, meets test 5;
- X_{2a} monovalent radical, such that the corresponding precursor of B_1 $-T_{BII}-X_{2a}$ meets test 5 but not test 4, precursor wherein the T_{BII} free valence is saturated with $-OZ$, $-Z$ or with $-Z^I-N-Z^{II}$, $-Z^I$ and Z^{II} being equal or different and having the Z values as defined below, depending on whether $T_{BII} = CO$ or X , in connection with the tI and tII values;
- the drug $A = R-T_1-$, wherein the free valence is

saturated as indicated hereinafter:

- when $t' = 0$ with:
 - O-Z wherein Z = H or R_{1a} , R_{1a} being a linear or branched when possible C_1-C_{10} alkyl, preferably C_1-C_5 , or with
 - Z^I-N-Z^{II} , Z^I and Z^{II} being as above defined;
- when $t = 0$ with -Z, wherein Z is as above defined, with the proviso that the drug is not a steroid,

is such as to meet at least one of tests 1-3;

wherein test 1 (NEM) is a test in vivo carried out on four groups of rats (each formed by 10 rats), the controls (two groups) and the treated (two groups) of which one group of the controls and one group of the treated respectively are administered with one dose of 25 mg/kg s.c. of N-ethylmaleimide (NEM), the controls being treated with the carrier and the treated groups with the carrier + the drug of formula $A = R-T_1$ wherein the free valence is saturated as above indicated, administering the drug at a dose equivalent to the maximum one tolerated by the rats that did not receive NEM, i.e. the highest dose administrable to the animal at which there is no manifest toxicity, i.e. such as to be symptomatologically observable; the drug complies

with test 1, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in the group treated with NEM + carrier + drug are observed gastrointestinal damages greater than those of the group treated with the carrier, or of the group treated with the carrier + drug, or of the group treated with the carrier + NEM;

wherein test 2 (CIP) is a test in vitro wherein human endothelial cells from the umbilical vein are harvested under standard conditions, then divided into two groups (each group replicated five times), of which one is treated with a mixture of the drug 10^{-4} M concentration in the culture medium, the other group with the carrier; then cumene hydroperoxide (CIP) having a 5 mM concentration in the culture medium is added to each of the two groups; the drug meets test 2, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), if a statistically significant inhibition of the apoptosis (cellular damage) induced by CIP is not obtained with $p < 0.01$ with respect to the group treated with the carrier and CIP;

wherein test 3 (L-NAME) is a test in vivo

carried out on four groups of rats (each group formed by 10 rats) for 4 weeks and receiving drinking water, the controls (two groups) and the treated (two groups), of which one group of the controls and of the treated respectively receives in the above 4 weeks drinking water added of N- ω -nitro-L-arginine methyl ester (L-NAME) at a concentration of 400 mg/litre, the controls in the 4 weeks being administered with the carrier and the treated in the 4 weeks with the carrier + the drug, administering the carrier or the drug + carrier once a day, the drug being administered at the maximum dose tolerated by the group of rats not pretreated with L-NAME, i.e., the highest dose administrable to animals at which no manifest toxicity appears, i.e. such as to be symptomatologically observable; after the said 4 weeks, the water supply is stopped for 24 hours and then sacrificed, determining the blood pressure 1 hour before sacrifice, and after sacrifice of the rats determining the plasma glutamic pyruvic transaminase (GPT) after sacrifice, and examining the gastric tissue; the drug meets test 3, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when in the group of rats treated with L-NAME + carrier + drug, greater hepatic damages

(determined as higher values of GPT) and/or gastric and/or cardiovascular damages (determined as higher values of blood-pressure) are found in comparison in comparison respectively with the group treated with the carrier alone, or with the group treated with the carrier + drug, or with the group treated with the carrier + L-NAME;

wherein test 4, which must not be met by the precursors of B or B₁ with the free valences saturated as above defined, is the following: it is an analytical determination carried out by adding portions of methanol solutions of the precursor of B or B₁ at a 10⁻⁴ M concentration, to a methanol solution of DPPH (2,2-diphenyl-1-picryl hydrazyl - free radical); after having maintained the solution at room temperature away from light for 30 minutes, it is read the absorbance at the wave length of 517 nm of the test solution and of a solution containing only DPPH in the same amount as in the test solution; and then the inhibition induced by the precursor towards the radical production by DPPH is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance

values of the solution containing the test compound + DPPH and that of the solution containing only DPPH. The criterium for acceptance of the compounds according to this test is the following: test 4 is met by precursor compounds if the inhibition percentage as above defined is higher than or equal to 50%; the precursor of B or B₁ must not meet test 4;

wherein test 5 is an analytical determination carried out by adding aliquots of 10^{-4} M methanol solutions of the precursor of B or B₁ or of C = -T_C-Y-H, having the free valence saturated as above indicated, to a solution formed by admixing a 2 mM solution of desoxyribose in water with 100 mM of phosphate buffer and 1 mM of the salt Fe^{II}(NH₄)₂(SO₄)₂; after having thermostatted the solution at 37°C for one hour, are added, in the order, aliquots of aqueous solutions of trichloroacetic acid 2.8% and of thiobarbituric acid 0.5 M, heating is effected at 100°C for 15 minutes and the absorbance of the solutions is then read at 532 nm; the inhibition induced by the precursor of B or B₁ or C = -T_C-Y-H in the confront of radical production by Fe^{II} is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound and the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage as above defined of the precursor of B or B_1 or $C = -T_c-Y-H$ is higher than or equal to 50%;

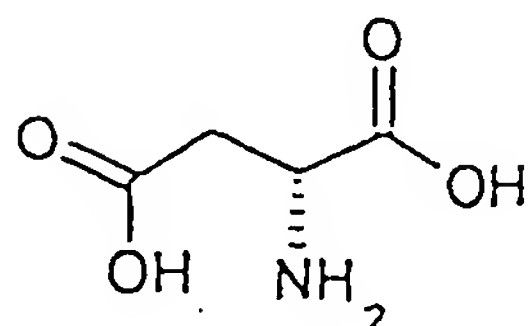
provided that in the compounds of formula (I) the following drugs under the following conditions are excluded:

- when $bo = 0$ and $C = -T_c-Y_0-$, wherein the free valence of Y_0 is saturated as above indicated, $s = 2$, the drug of formula $A = R-T_1-$, as above defined, has not to belong to the following classes: drugs for use in incontinence, antithrombotic drugs (ACE-inhibitors), prostaglandins;
- when $bo = 0$ and $C = -T_c-Y-$, wherein the free valence of Y is saturated as above indicated, and $s = 2$, the drugs of formula $A = R-T_1-$ belonging to the class of non steroid antiinflammatory drugs.

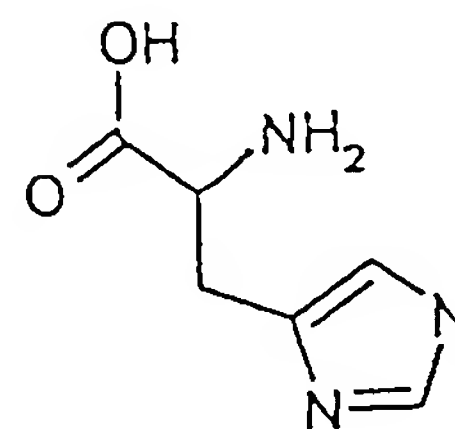
2. Compounds according to claim 1 wherein the precursor compound of B or B_1 is selected from the following compounds:

- Aminoacids: aspartic acid (PI), histidine (PII),

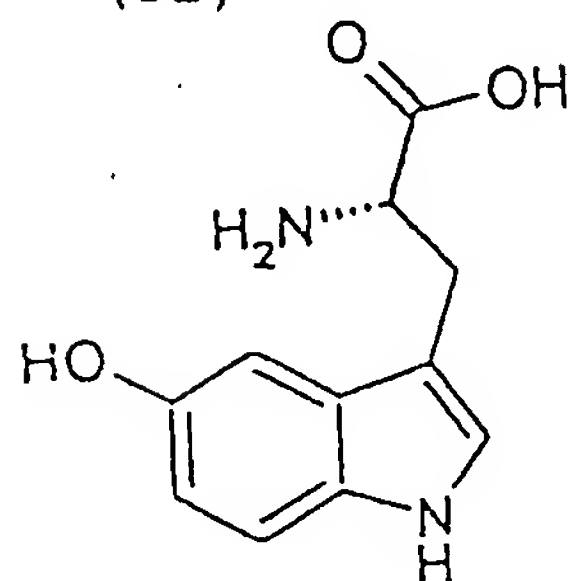
5-hydroxytryptophan (PIII), 4-thiazolidincarboxylic acid (PIV), 2-oxo-4-thiazolidincarboxylic acid (PV)



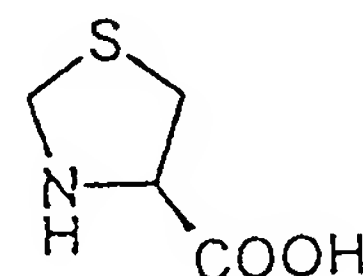
(PI)



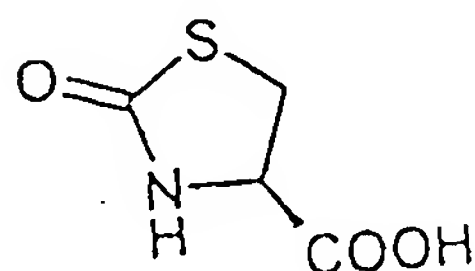
(PII)



(PIII)



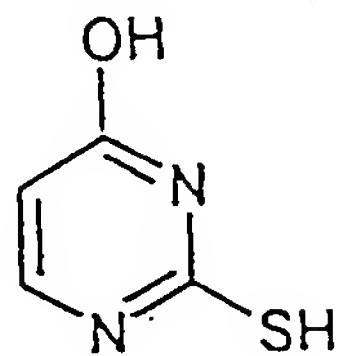
(PIV)



(PV)

mono and polyalcohols or thiols: 2-thiouracil (QI), 2-mercaptoethanol (QII), esperidine (QIII), secalciferol (QIV), 1- α -OH vitamin D2 (QV), flocalcitriol (QVI), 22-oxacalcitriol (QVII), the vitamin D3 derivative esterified with the vitamin A radical (QVIII), the formula (QIX) compound, 24,28-methylene-1 α -hydroxyvitamin D2 (QX) the compound derived from 1 α ,25-dihydroxyvitamin D2 (QXI), 2-mer-

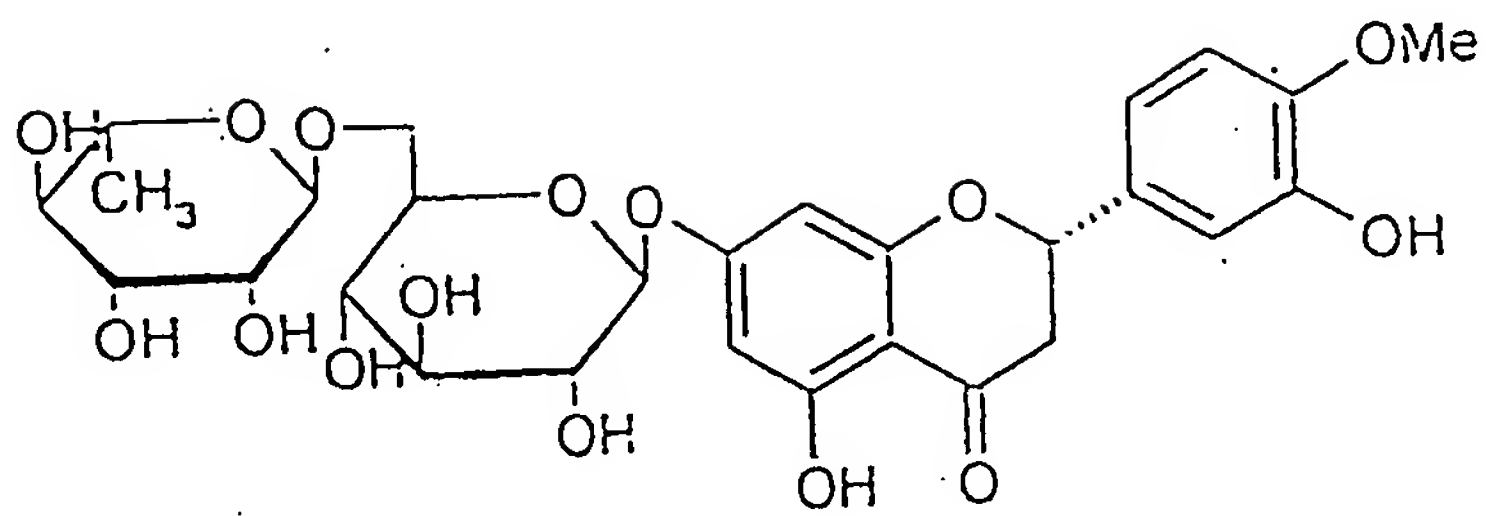
captoimidazol (QXII)



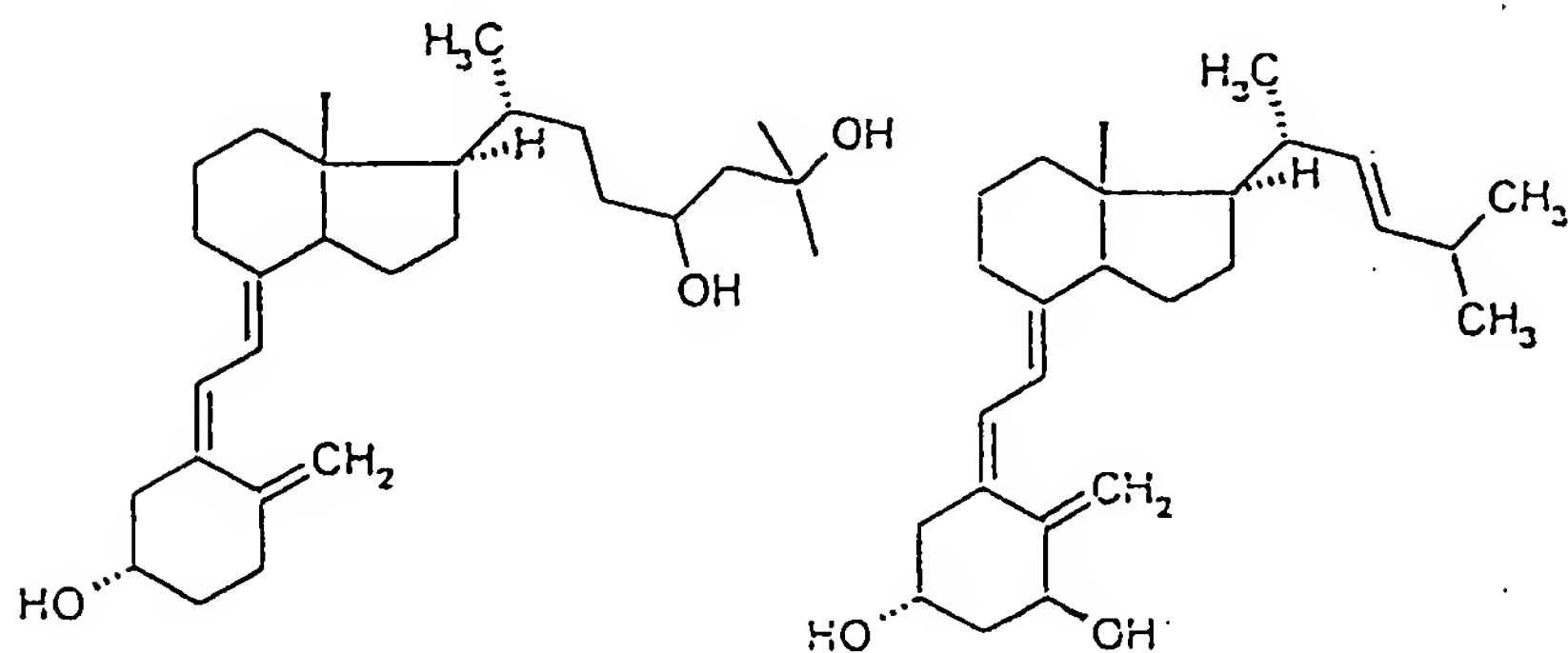
(QI)



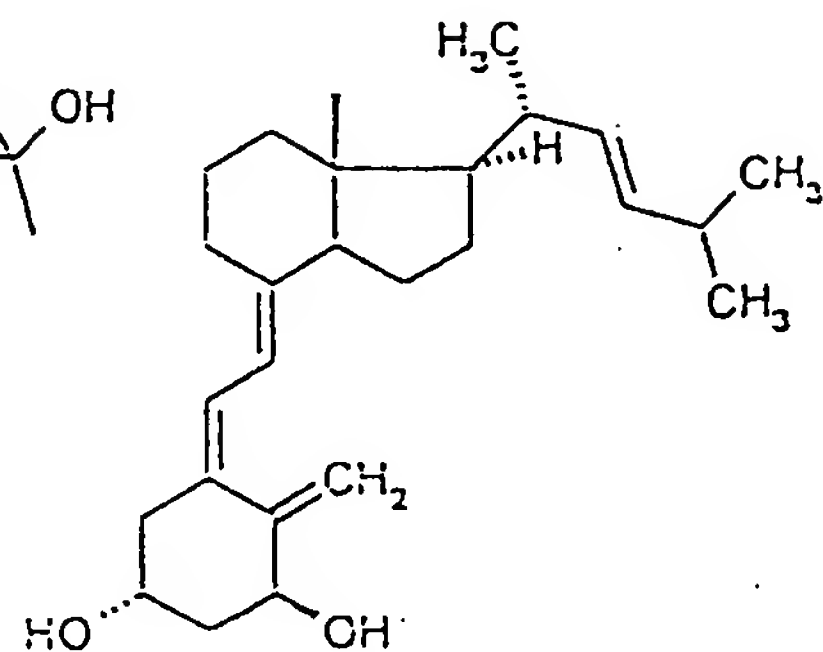
(QII)



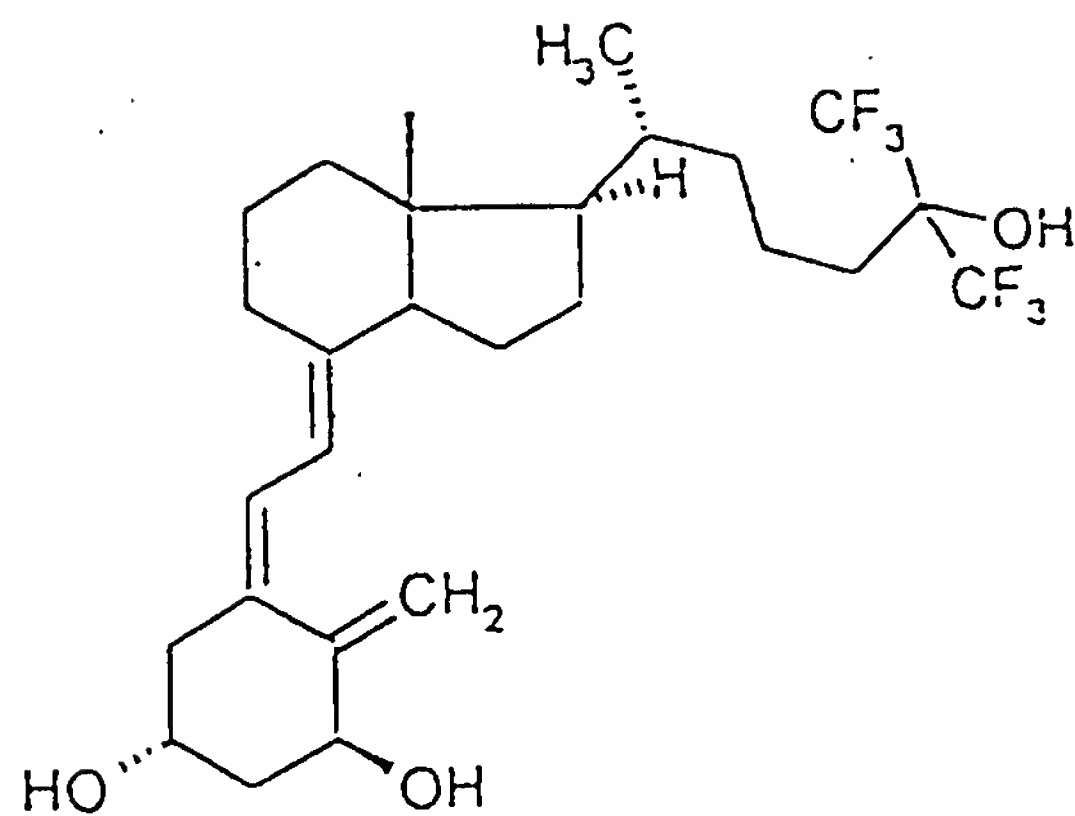
(QIII)



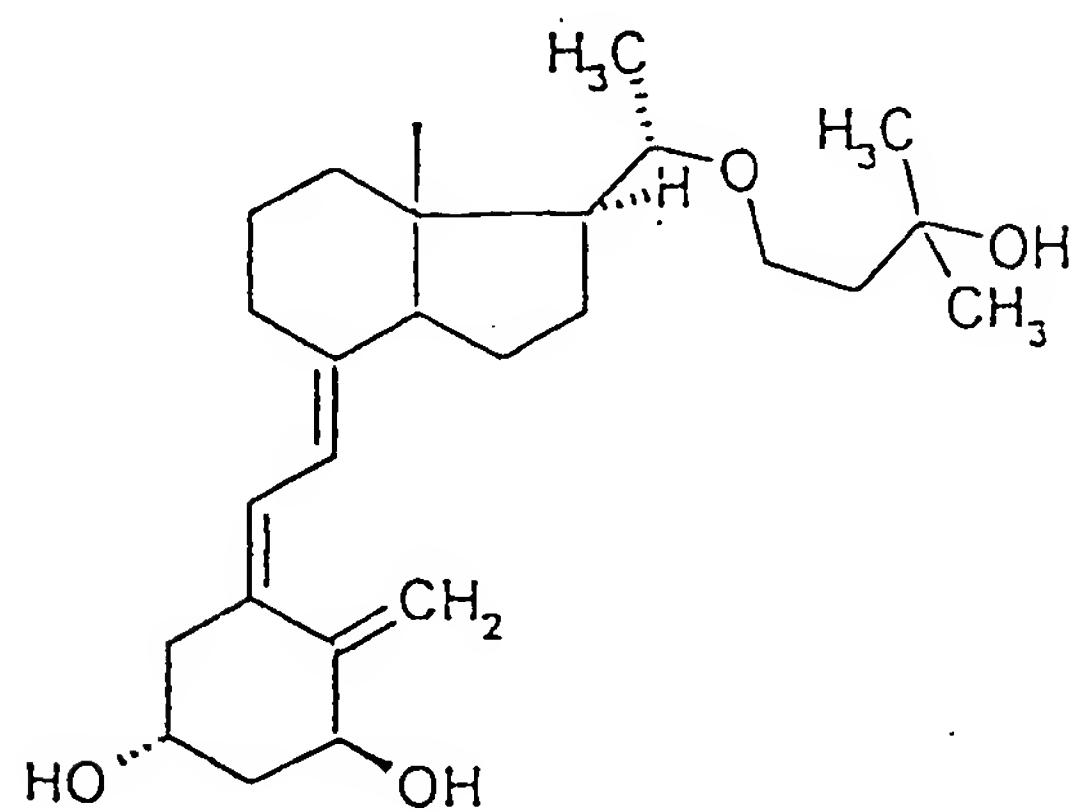
(QIV)



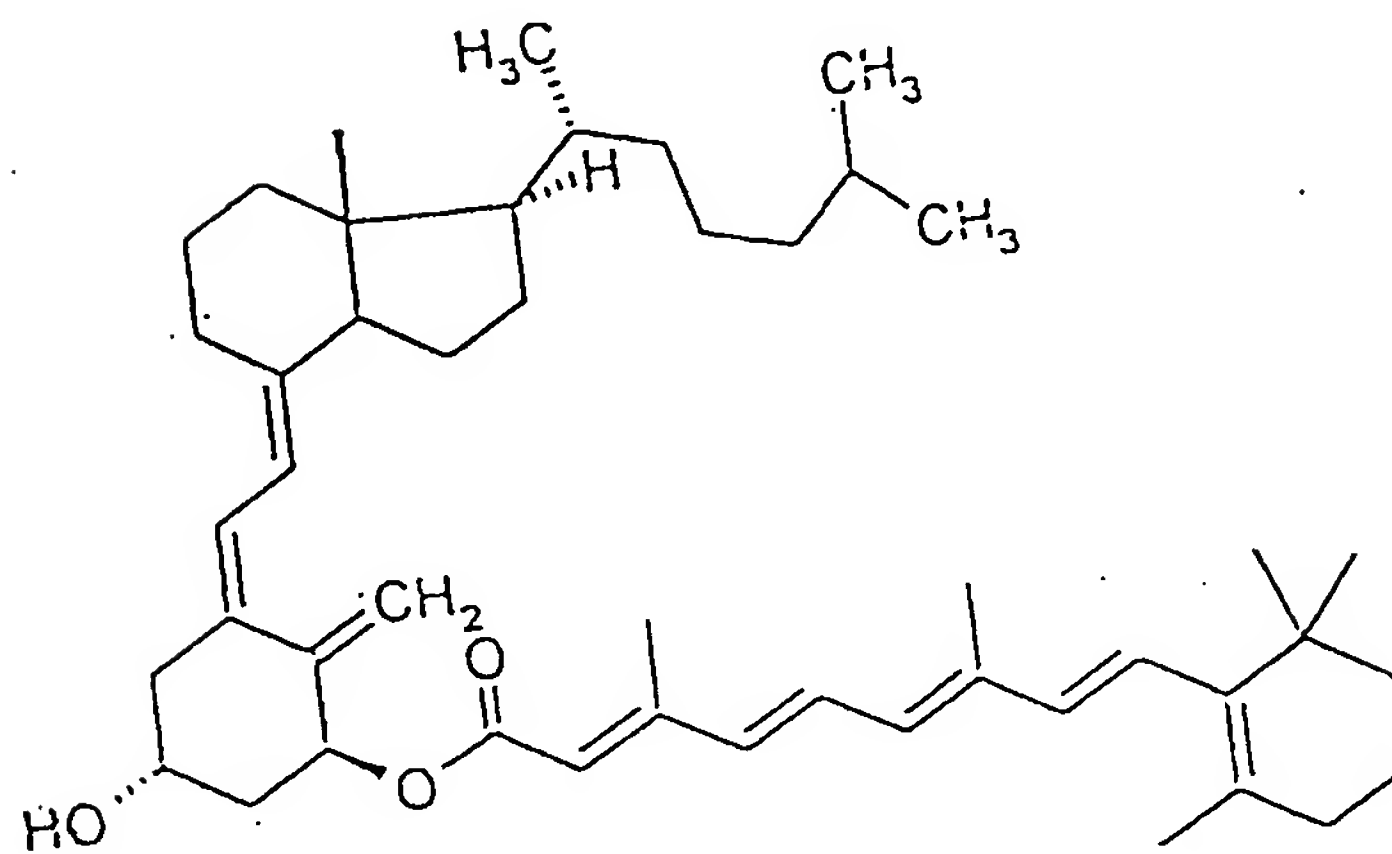
(QV)



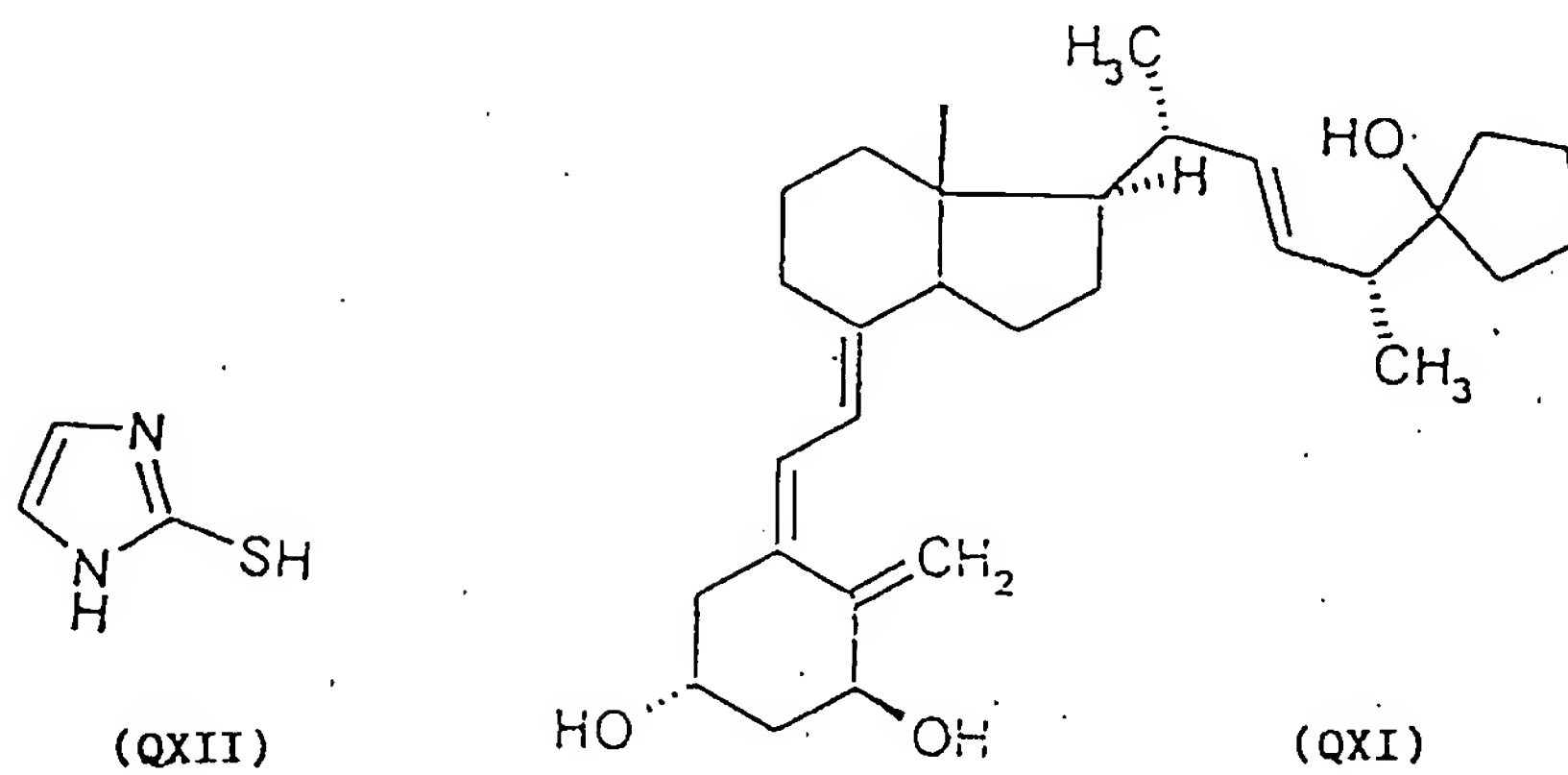
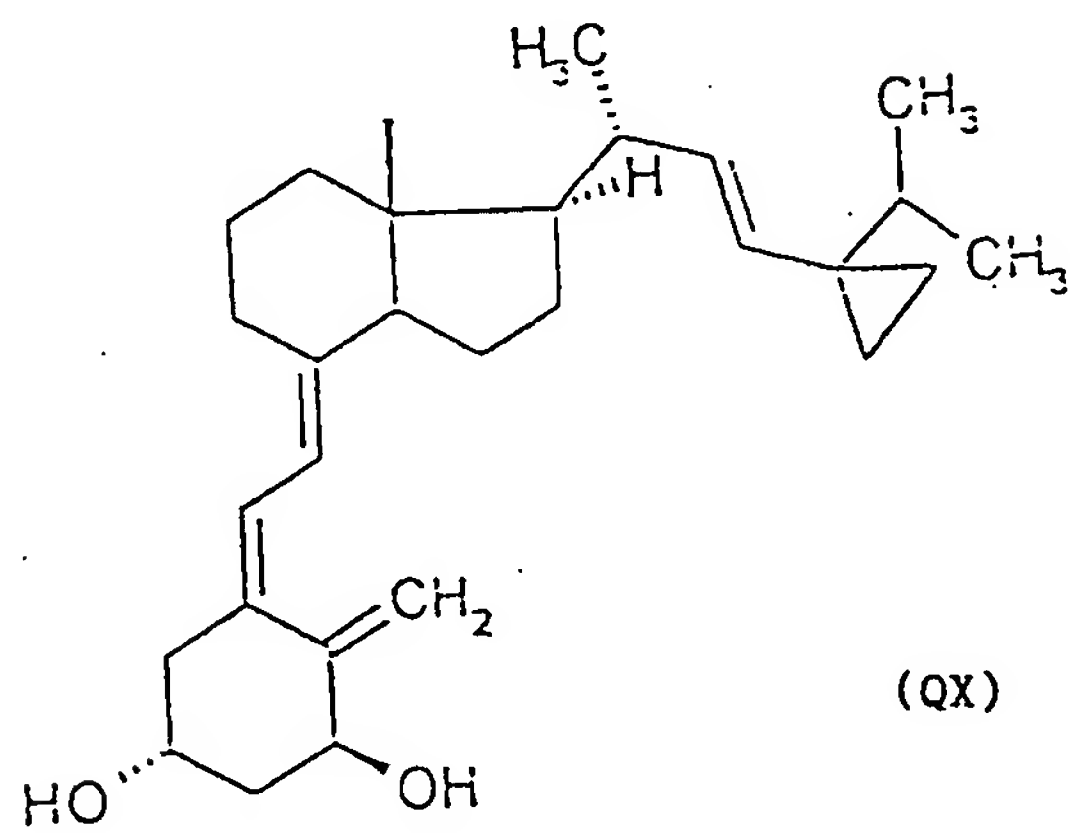
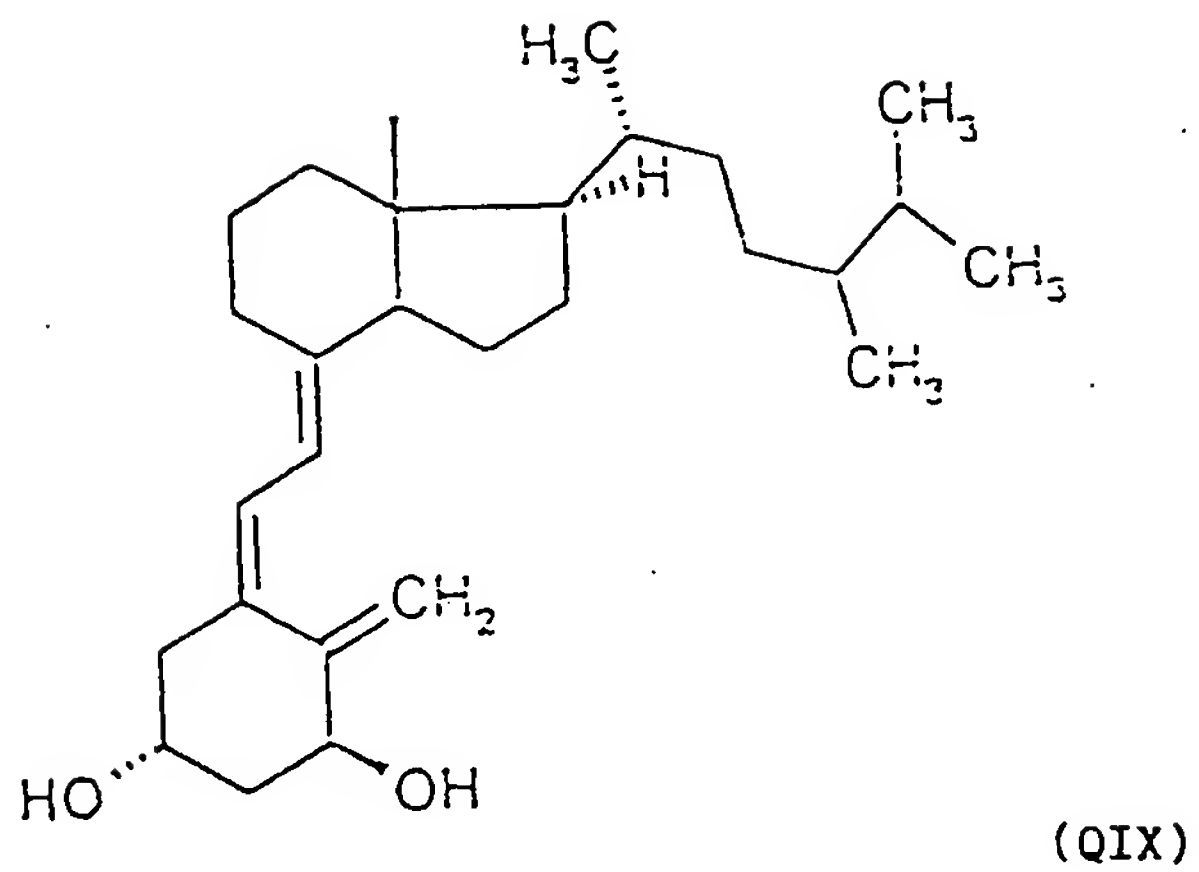
(QVI)



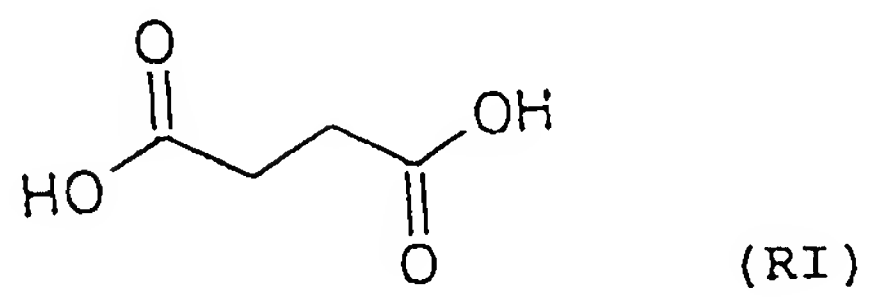
(QVII)



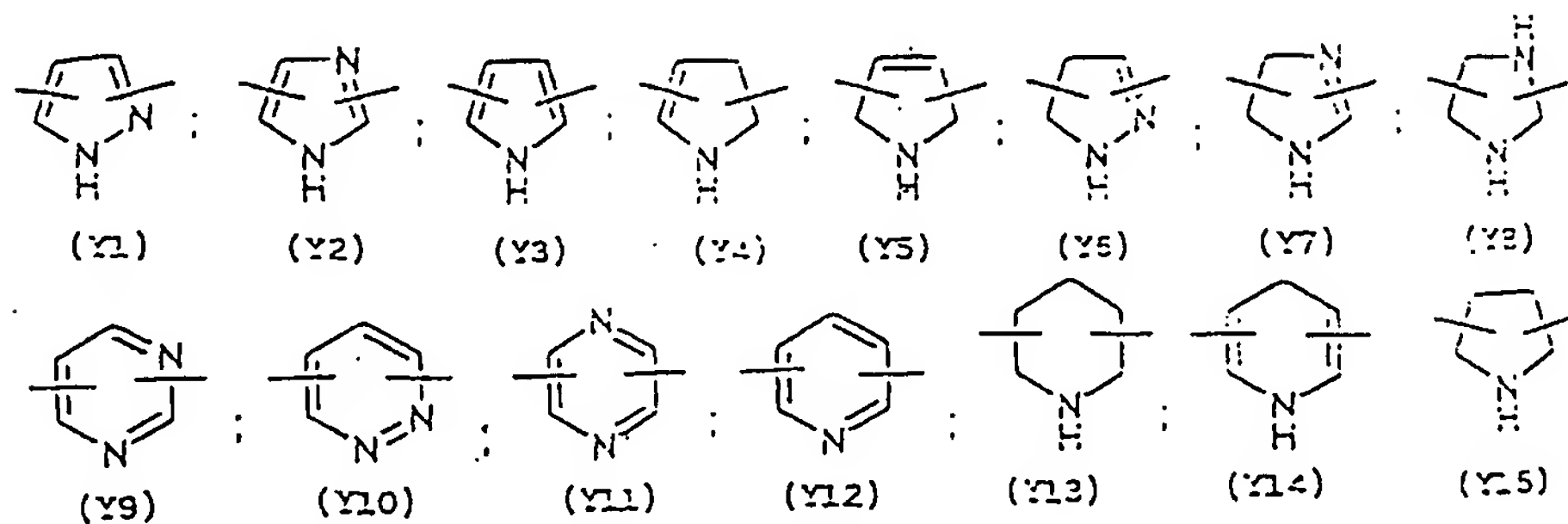
(QVIII)



succinic acid (RI)



3. Compounds according to claims 1-2, wherein in formula (III) Y^3 is selected from the following:



4. Compounds according to claim 3, wherein Y^3 is Y12 (pyridyl), substituted in positions 2 and 6.
5. Compounds according to claims 1-4 wherein the precursor drugs of the compounds of formula (I) and (II) are selected from the following: anti-inflammatory, analgesic drugs, bronchodilators and drugs active on the cholinergic system, expectorant-mucolytic drugs, antiasthmatic-antiallergic, antihistaminic drugs, ACE-inhibitors, beta-blockers, antithrombotic drugs, vasodilators, antidiabetic, antitumoral, antiulcer, antihyperlipidemic, antibiotic, antiviral drugs, bony reabsorption inhibitors, antidementia drugs.
6. Compounds according to claim 5, wherein the precursor drugs are selected from the following:
anti-inflammatory drugs: aceclofenac, acemetacin, acetylsalicylic acid, 5-aminoacetylsalicylic acid, alclofenac,

alminoprofen, amfenac, bendazac, bermoprofen, α -bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen, cinmetacin, clidanac, clopirac, sodium diclofenac, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, olsalazine, oxaceprol, oxaprozin, oxyphenbutazone, parsalmide, perisoxal, phenyl acetylsalicylate, pyrazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicylamide O-acetic acid, salicylsulphuric acid, salsalate, sulindac, suprofen, suxibuzone, tenoxicam, tiaprofenic acid, tiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepirac, tomoxiprol; analgesic drugs: acetaminophen, acetaminosalol, aminochlorthenoxazin, acetylsalicylic 2-amino-4-picoline acid, acetylsalicylsalicylic acid, anileridine, benoxaprofen benzylmorphine, 5-bromosalicylic acetate acid, bucetin, buprenorphine, butorphanol, capsaicine, cinchophen, ciramadol, clometacin, clonixin, codeine, desomorphine,

dezocine, dihydrocodeine, dihydromorphine, dimepheptanol, dipyroceryl, eptazocine, ethoxazene, ethylmorphine, eugenol, floctafenine, fosfosal, glafenine, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, p-lactophenetide, levorphanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nicomorphine, norlevorphanol, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, phenocoll, phenoperidine, phenylbutazone, phenylsalicylate, phenylramidol, salicin, salicylamide, tiorphan, tramadol, diacerein, actarit;

bronchodilators and drugs active on the cholinergic system: acefylline, albuterol, bambuterol, bamifylline, bevonium methyl sulphate, bitolterol, carbuterol, clenbuterol, chlorprenaline, dioxethedrine, difylline, ephedrine, epinephrine, eprozinol, etafredine, ethylnorepinephrine, etofylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium bromide, isoetharine, isoprotenerol, mabuterol, metaproterenol, oxybutynin, oxitropium bromide, pirbuterol, procaterol, protokylol, proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, 1-teobromineacetic acid, tiotropium bromide, tretoquinol, tulobuterol, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetrahydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: ambroxol, bromhexine, domio-

dol, erdosteine, guaiacol, guaifenesin, iodinated glycerol, letosteine, mesna, sobrerol, stepronin, terpin, tiopronin;

antiasthmatic/antiallergic antihistaminic drugs:

acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam, chromoglycate, chromolyn, epinastine, fexofenadine, formoterol, histamine, hydroxyzine, levocabastine, lodoxamide, mabuterol, metron s, montelukast, nedocromil, repirinast, seratrovast, suplatast tosylate, terfenadine, tiaramide, urushiol, bromhexine;

ACE-inhibitors: alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, losartan, moveltipril, naphthopidil, perindopril, quinapril, ramipril, spirapril, temocapril,trandolapril, urapidil;

beta-blockers: acebutolol, alprenolol, amosulalol, arotinolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, dilevalol, epanolol, esmolol, indenolol, labetalol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipridalol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol;

antithrombotic and vasoactive drugs: acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betahistine, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, dalteparin, dipyridamole, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, heparin, lamifiban, midodrine, nadroparin, nicotinyl alcohol, nylidrin, ozagrel, perhexiline, phenylpropanolamine, prenylamine, pavaroline, reviparin sodium salt, ridogrel, suloctidil, tinofedrine, tinzaparin, triflusal, xanthinol niacinate;

antidiabetic drugs: acarbose, carbutamide, glibornuride glybuthiazol(e), miglitol, repaglinide, troglitazone, 1-butyl-3-metanyl-urea, tolrestat, nicotinamide;

antitumoral drugs: ancitabine, anthramycin, azacitidine, azaserine, 6-azauridine, bicalutamide, carubicin, carzinophilin, chlorambucil, chlorozotocin, cytarabine, daunorubicin, defosfamide, demecolcine, denopterin, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicin, droloxifene, edatrexate, eflornithine, enocitabine, epirubicin, epitiostanol, ethanidazole, etoposide, fenretinide, fludarabine, fluorouracil, gemcitabine, hexestrol, idarubicin, lonidamine, mannomustine, melphalan, menogaril, 6-mercaptopurine, methotrexate,

mitobronitol, mitolactol, mitomycins, mitoxantrone, mopidamol, mycophenolic acid, ninopterin, nogalamycin, paclitaxel, pentostatin, pirarubicin, piritrexim, plicamycin, podophyllic acid, porfimer sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, thiamiprine, thioguanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicin;

antiulcer drugs: ϵ -acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecabet, enprostil, esaprazole, irsogladine, misoprostol, omeprazole, ornoprostil, pantoprazole, plaunotol, rioprostil, rosaprostol, rotraxate, sofalcone, trimoprostil;

anti-hyperlipidemic drugs: atorvastatin, cilastatin, dermostatin, fluvastatin, lovastatin, mevastatin, nystatin, pentostatin, pepstatin, privastatin sodium salt, simvastatin;

antibiotics: amdinocillin, amoxicillin, ampicillin, apalcillin, apicycline, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoylpas, benzyl penicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone,

cefazolin, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin, ceftazopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteteram, ceftetazole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephradine sodium, cephalixin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cephalixin sodium, cephradine, chloramphenicol, chlortetracycline, cinoxacin, ciprofloxacin, clavulanic acid, clometocillin, cloxacillin, cyclacillin, cycloserine, demeclocycline, dicloxacillin, epicillin, fenbecillin, flomoxef, floxacillin, hetacillin, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, meclocycline, meropenem, metampicillin, methacycline, methicillin sodium, mezlocillin, minocycline, moxalactam, mupirocin, myxin, negamycin, novobiocin, oxacillin, panipenem, penicillin G potassium salt, penicillin N, penicillin O, penicillin V, phenethicillin potassium salt, pipacycline, piperacillin, pirlimycin, porfiromycin, propycillin, quinacillin, ritipenem, rolitetracycline, sancycline, sedecamycin, spectinomycin, sulbactam, sulbenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidin,

azithromycin, clarithromycin, dirythromycin, enviomycin, erythromycin, josamycin, midecamycin, miokamycin, oleandomycin, rifabutine, rifamide, rifamycin, rifaximin, rokitamycin, spiramycin, troleandomycin, viomycin, virginiamycin;

amikacin, apramycin, arbekacin, dibekacin, dihydrostreptomycin, fortimicins, gentamicin, micronomicin, neomycin, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin; bacampicillin, cefcapene pivoxil, cefpodoxime proxetil, panipenem, pivampicillin, pivcefalexin, sultamicillin, talampicillin;

carbomycin, clindamycin, lincomycin, mikamycin, rosaramicin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, flumequine, grepafloxacin, lomefloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rufloxacin, sparfloxacin, tosufloxacin, trovafloxacin, clomocycline, guamecycline, oxytetracycline, nifurpirinol, nifurprazine;

p-aminosalicylic acid, p-aminosalicylic acid hydrazide, clofazimine, deoxydihydrostreptomycin, ethambutol, glyconiazide, isoniazid, opiniazide, phenyl aminosalicylate, rifampin, rifapentine, salinazid, 4-4'-sulfynyldianiline,

acediasulfone, dapsone, succisulfone, p-sulfanilylbenzyl amine, thiazolsulfone, acetyl sulfamethoxypyrazine, mafenide, 4'-(methylsulfamoyl)sulfanilanilide, salazosulfadimidine, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadiazamide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 2-p-sulfanilylanilinoethanol, N⁴-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfisomidine, sulfisoxazole, 4-sulfanilamido salicylic acid; negamycin, carumonan, cloxyquin, nitroxoline, arginine, metronidazole;

antiviral drugs: acyclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, indanavir, kethoxal, lamivudine, MADU, penciclovir, podophyllotoxin, ribavirin, rimantadine, saquinavir, sorivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine;

bone resorption inhibitors: alendronic acid, butedronic acid, etidronic acid, oxydronic acid, pamidronic acid, risedronic acid;

antidementia drugs: amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

7. Compounds according to claims 5-6, wherein the precursor drugs are selected from the following:

anti-inflammatory drugs: acetylsalicylic acid, 5-aminoacetylsalicylic acid, carprofen, diclofenac sodium, diflunisal, etodolac, flufenamic acid, flunixin, flurbiprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, naproxen, niflumic acid, olsalazine, piroxicam, salsalate, sulindac, suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, tolmetin, zomepirac, tomoxiprol;

analgesic drugs: acetaminophen, acetylsalicylsalicylic acid, benoxaprofen, buprenorphine, butorphanol, capsaicin, diacerein, dihydrocodeine, ethylmorphine, eugenol, phenylbutazone, meptazinol, morphine, nalbuphine, pentazocine, thiorphan, tramadol, actarit;

bronchodilators and drugs active on the cholinergic system: albuterol, carbuterol, clenbuterol, diphylline, etophylline, fenoterol, ipratropium bromide, metaprotere-

nol, oxybutynin, pirbuterol, salmeterol, terbutaline, tiotropium bromide, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetrahydro-pyridin-4-yl methyl)acetamide;

expectorant/mucolytic drugs: ambroxol, bromexine, guaia-col, sobrerol;

antiasthmatic/antiallergic antihistaminic drugs:

cetirizine, chromoglycate, histamine, levocabastine, lodoxamide, montelukast, terfenadine, bromexine;

ACE-inhibitors: captopril, enalapril, lisinopril, losartan, ramipril;

beta blockers: alprenolol, atenolol, bupranolol, labetalol, metipranolol, metoprolol, pindolol, propranolol, timolol;

antithrombotic and vasoactive drugs: acetylsalicylic acid, acetorphan, argatroban, clopidogrel, dalteparin, dipyridamole, enoxaparin, heparin, iloprost, midodrine, ozagrel, phenylpropanolamine, trifusal;

antidiabetic drugs: tolrestat, nicotinamide;

antitumoral drugs: anthramycin, daunorubicin, doxorubicin, epirubicin, fluorouracyl, methotrexate, vinblastine;

antiulcer drugs: cimetidine, omeprazole, pantoprazole;

antihyperlipidemic drugs: lovastatin, pravastatin sodium, simvastatin;

antibiotics drugs: amoxicillin, ampicillin, aztreonam,

biapenem, carbenecillin, cefaclor, cefadroxil, cefamandole, cefatrizine, ceftioxin, clavulanic acid, dicloxacillin, imipenem, meclocycline, methacycline, moxalactam, panipenem, sulbactam, azithromycin, erythromycin, josamycin, miokamycin, rifabutine, rifamide, rifamycin, gentamicin, paromomycin, sisomicin, bacampicillin, carbomycin, clindamycin, ciprofloxacin, clinafloxacin, difloxacin, enrofloxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pipemidic acid, apicycline, clomocycline, oxytetracycline, nifurpirinol, nifurprazine, isoniazid, rifampin, rifapentine, dapson, thiazolsulfone, sulfamethoxazole, sulfamoxole, metronidazole, arginine;

antiviral drugs: aciclovir, famciclovir, ganciclovir, penciclovir, ribavirin, vidarabine, zidovudine;

bone resorption inhibitors: alendronic acid, etidronic acid, pamidronic acid.

8. Compounds or salts, or their compositions according to claims 1-7 for use as drugs;

provided that in the compounds of formula (I) the following drugs under the following conditions are excluded:

- when $b_0 = 0$ and $C = -T_C-Y_0-$, wherein the free valence of Y_0 is saturated as above indicated, $s = 2$, the drug of formula $A = R-T_1-$, as above defined, has not to

belong to the following classes: drugs for use in incontinence, antithrombotic drugs (ACE-inhibitors), prostaglandins;

- when $b_0 = 0$ and $C = -T_C-Y-$, wherein the free valence of Y is saturated as above indicated, and $s = 2$, the drugs of formula $A = R-T_1-$ belonging to the class of non steroid antiinflammatory drugs.

9. Use of compounds or salts, or compositions thereof according to claims 1-7 for the preparation of drugs for the therapeutic stress-oxidative application.

- when $b_0 = 0$ and $C = -T_C-Y_0-$, wherein the free valence of Y_0 is saturated as above indicated, $s = 2$, the drugs of formula $A = R-T_1-$ can be drugs for use in incontinence, antithrombotic drugs, prostaglandin;

- when $b_0 = 0$, $C = -T_C-Y-$, wherein the free valence of Y is saturated as above indicated, $s = 2$, the drugs can be non steroid antiinflammatory drugs.

10. Pharmaceutical formulations containing as active principle the compounds or their salts of claims 1-7.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07J 41/00, A61K 31/575	A2	(11) International Publication Number: WO 00/61604 (43) International Publication Date: 19 October 2000 (19.10.00)
(21) International Application Number: PCT/EP00/03238 (22) International Filing Date: 11 April 2000 (11.04.00) (30) Priority Data: MI99A000751 13 April 1999 (13.04.99) IT (71) Applicant (for all designated States except US): NICOX S.A. [FR/FR]; 45, avenue Kléber, F-75116 Paris (FR). (72) Inventor; and (75) Inventor/Applicant (for US only): DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I-20052 Monza (IT). (74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni, 2, I-20129 Milano (IT).		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.
(54) Title: PHARMACEUTICAL COMPOUNDS <div style="text-align: center;"> $A-(B)_{b0}-C-N(O)_s \quad (I)$ </div> <div style="text-align: center;"> $\begin{array}{c} A-C_1-B_1 \\ \\ N(O)_s \end{array} \quad (II)$ </div> (57) Abstract Steroidal compounds or their salts having general formulas (I) and (II) wherein: s is an integer equal to 1 or 2, preferably s = 2; b0 = 0 or 1; A = R-, wherein R is the steroidal drug radical, C and C ₁ are two bivalent radicals. The precursors of the radicals B and B ₁ are such as to meet the pharmacological tests reported in the description.		

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"PHARMACEUTICAL COMPOUNDS"

* * * * *

The present invention relates to novel steroidal compounds for systemic use and non systemic use, and their compositions, to be used in the conditions of oxidative stress and/or endothelial dysfunctions. Specifically it relates to compounds with a steroidal structure having antiinflammatory, immunodepressive and angiostatic activity (the so called antiinflammatory steroids), or gastrointestinal activity.

The compounds according to the present invention result therapeutically useful in the treatment of morbid conditions wherein the steroidal products are generally used with greater benefit, in terms both of a better tolerability and/or efficacy.

By oxidative stress it is meant the generation of free radicals or radicalic compounds, which causes injury both of the cell and of that of the surrounding tissue (Pathophysiology: the biological basis for disease in adults and children, McCance & Huether 1998 pages 48-54).

By endothelial dysfunctions are meant those relating to the vasal endothelium. The damage of the vasal endothelium is known as one of those important events that can bring about a series of pathological processes affecting various organs and

body apparatuses, as described hereinafter (Pathophysiology: The biological basis for disease in adults and children, McCance & Huether 1998 page 1025).

As known, the oxidative stress and/or the endothelial dysfunctions are associated to various pathologies as reported hereinafter. The oxidative stress can also be caused by toxicity of a great variety of drugs, which significantly affects their performances.

Said pathological events are of a chronic, debilitating character and are very often typical of the elderly. As already said, in said pathological conditions the drugs used show a remarkably worsened performance.

Examples of pathological situations caused by the oxidative stress and/or by the endothelial dysfunctions, or present in elderly, are the following:

- For the cardiovascular system: myocardial and vascular ischaemia in general, hypertension, stroke, arteriosclerosis, etc.
- For the connective tissue: rheumatoid arthritis and connected inflammatory diseases, etc.
- For the pulmonary system: asthma and connected inflammatory diseases, etc.
- For the gastrointestinal system: ulcerative and non ulcerative dyspepsias, intestinal inflammatory diseases, etc.

- For the central nervous system: Alzheimer disease, etc.
- For the urogenital system: impotence, incontinence.
- For the cutaneous system: eczema, neurodermatitis, acne.
- The infective diseases in general (ref.: Schwarz-KB, Brady "Oxidative stress during viral infection: A review" Free radical Biol. Med. 21/5, 641-649 1996).

Further the ageing process can be considered as a true pathologic condition (ref. Pathophysiology: the biological basis for disease in adults and children, pages 71-77).

The known drugs when administered to patients having pathologies associated to oxidative stress and/or endothelial dysfunctions, show a lower efficacy and/or higher toxicity.

This happens for example with steroids.

Drug research is directed to find new molecules having an improved therapeutic index (efficacy/toxicity ratio) or a lower risk/benefit ratio, also for pathological conditions as those above mentioned, wherein the therapeutic index of a great number of drugs results lowered. In fact in the above mentioned conditions of oxidative stress and/or endothelial dysfunctions, many drugs show a lower activity and/or higher toxicity.

It is well known that steroids represent a first choice pharmacological intervention in the therapy of inflammatory diseases. This class of drugs, among which can be mentioned for example hydrocortisone, cortisone, prednisone, prednisolone, fludrocortisone, desoxycorticosterone, metilprednisolone,

triamcinolone, paramethasone, betamethasone, dexamethasone, triamcinolone acetonide, fluocinolone acetonide, beclomethasone, acetoxypregnelone, etc., elicits remarkable pharmaco-toxicological effects on different organs, and for this reason both their clinical use and its interruption cause a series of side effects, some of which very serious. See for example Goodman & Gilman, "The pharmaceutical Basis of Therapeutics" 9th ed., pages 1459-1465, 1996.

Among said toxic effects can be mentioned those affecting the bone tissue leading to an altered cellular metabolism and an high osteoporosis incidence; those affecting the cardiovascular system, generating an hypertensive response; those affecting the gastrointestinal apparatus giving gastric damages.

See for example Martindale "The extrapharmacopoeia", 30th ed., pages 712-723, 1993.

To the class of steroidal drugs belong also biliary acids, that have been used in the therapy of hepatic disorders and in biliary colics. Ursodesoxycholic acid is also used in some hepatic dysfunctions (hepatic cirrhosis of biliary origin, etc.). Their tolerability is strongly worsened in the presence of gastrointestinal complications (chronic hepatic damage, peptic ulcer, intestinal inflammation, etc.). Also in the case of biliary acids the oxidative stress remarkably affects drug performance: both the efficacy and the tolerability of

chenodeoxycholic and ursodesoxycholic acids are significantly reduced. In particular the unwanted effects on liver are found exalted. Among the steroidal compounds can be mentioned also estrogens for the treatment of dislipidaemias, hormonal troubles, female apparatus tumours treatment can be mentioned. Also said steroids show side effects as above mentioned, in particular at the hepatic level.

According to the above mentioned prior art it seems almost impossible to separate therapeutic activity from side effects, see Goodman et al, above mentioned, at p. 1474.

The steroidal compounds are completely different from the antiinflammatory non steroidal compounds from the chemical, pharmacological and biochemical point of view, since the pharmaco-toxicological mechanism of action of nonsteroidal antiinflammatory products is based on the inhibition of one or more of the cyclooxygenases (COX), while steroids do not influence COX and have more complex pharmaco-toxicological mechanisms of action not yet fully cleared.

Indeed it is well known that these two groups of drugs are classified in different classes in the pharmacopoeias.

The need was felt to have available steroids showing an improved therapeutic performance, i.e. endowed both of a lower toxicity and/or higher efficacy, so that they could be administered to patients in morbid conditions of oxidative stress and/or endothelial dysfunctions, without showing the

drawbacks of the drugs of the prior art.

It has been now surprisingly and unexpectedly found that the aforementioned technical problems shown in the administration of steroidal drugs to patients affected by oxidative stress and/or endothelial dysfunctions, or to the elderly in general, are solved by a new class of drugs as described hereinafter.

An object of the invention are steroidal compounds or their salts having the following general formulas (I) and (II):



wherein:

s = is an integer equal to 1 or 2, preferably s = 2;

b₀ = 0 or 1;

A = R-T₁-, wherein R is the steroidal drug radical as defined hereunder,

B = -T_B-X₂-T_{BI}- wherein

T_B and T_{BI} are equal or different;

T_B = (CO) when the reactive function in the precursor steroid is -OH; T_B = X when the reactive function in the precursor steroid is -COOH;

X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl having from 1 to 5 carbon atoms, or a free valence;

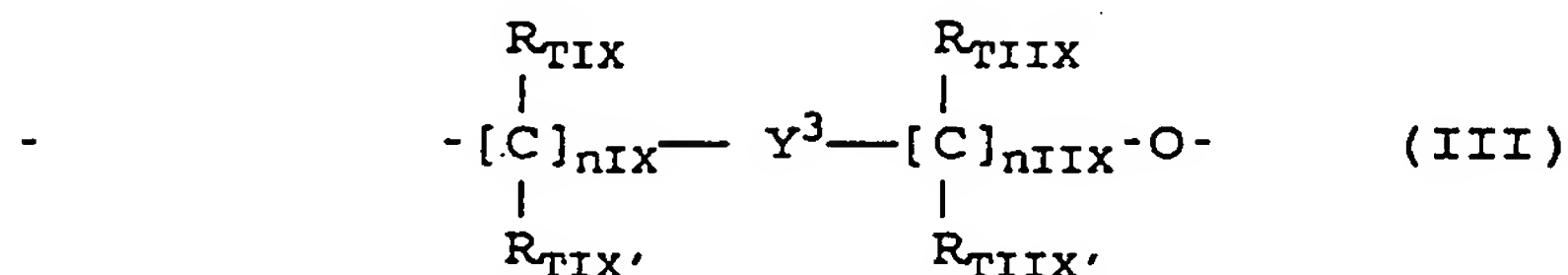
T_{BI} = (CO)_{tx} or (X)_{txx}, wherein tx and txx have the value of 0 or 1; with the proviso that tx = 1 when txx = 0, tx = 0 when txx = 1; X is as above defined;

X_2 is a bivalent bridging bond as defined hereunder;

C is the bivalent radical $-T_C-Y-$ wherein

$T_C = (CO)$ when $tx = 0$, $T_C = X$ when $txx = 0$, X being as above defined;

Y is:



wherein:

nIX is an integer between 0 and 3, preferably 1;

$nIIIX$ is an integer between 1 and 3, preferably 1;

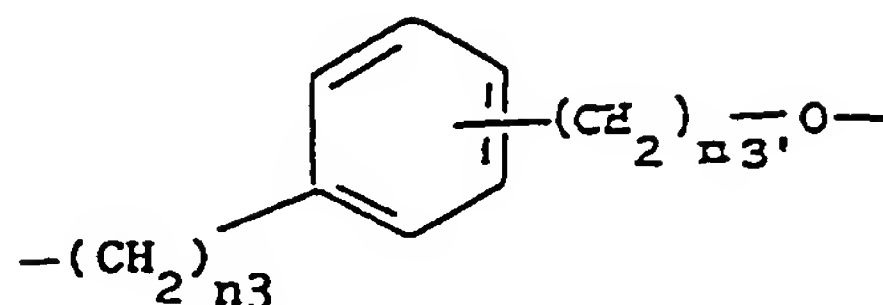
R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$, equal to or different from each other are H or a linear or branched C_1-C_4 alkyl; preferably R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$ are H.

Y^3 is a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen atom, preferably one or two nitrogen atoms, said ring having 5 or 6 atoms.

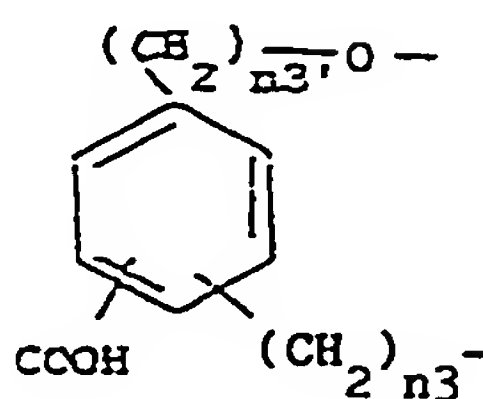
or Y is Y_0 , selected from the following:

- an alkyleneoxy group $R'O$ wherein R' is linear or branched when possible C_1-C_{20} , preferably having from 1 to 6 carbon atoms, most preferably 2-4 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylenic ring one or more carbon atoms can be substituted with heteroatoms, the ring

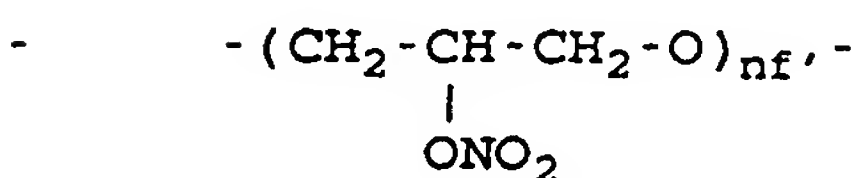
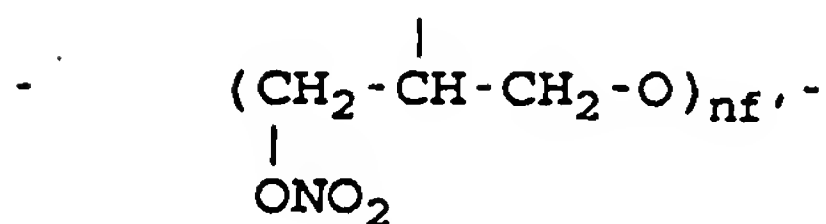
can have side chains of R' type, R' being as above defined; or



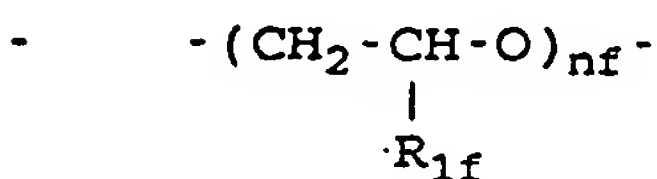
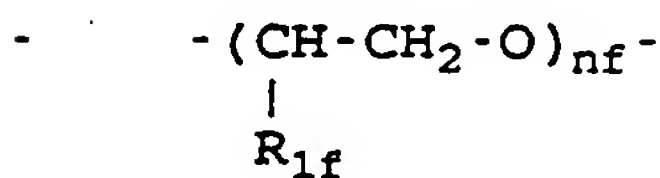
wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;



wherein n3 and n3' have the above mentioned meaning



wherein nf' is an integer from 1 to 6 preferably from 1 to 4;



wherein R_{1f} = H, CH₃ and nf is an integer from 1 to

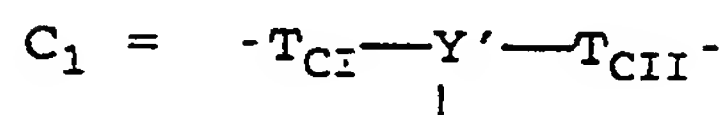
6; preferably from 1 to 4;

preferably $Y = -Y_0 = R'O-$ wherein R' is as above defined;

preferably R' is a C_1-C_6 alkylene;



wherein:



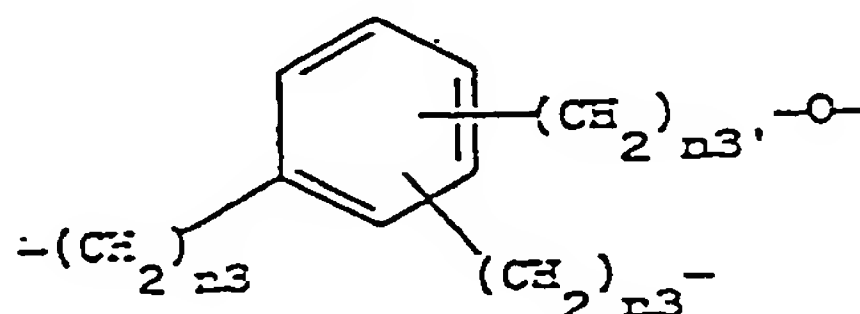
wherein T_{CI} and T_{CII} are equal or different,

$T_{CI} = (CO)$ when the reactive function of the precursor steroid is $-OH$, $T_{CI} = X$ when the reactive function of the precursor steroid is $-COOH$, X being as above defined;

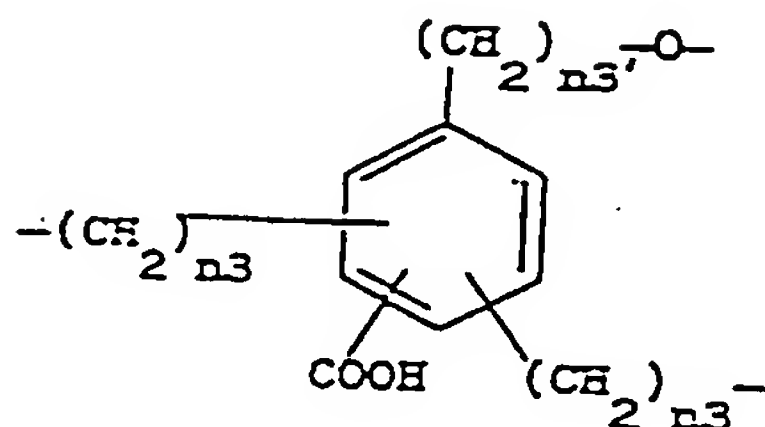
$T_{CII} = (CO)_{tI}$ or $(X)_{tII}$, wherein tI and tII have the 0 or 1 value; with the proviso that $tI = 1$ when $tII = 0$; $tI = 0$ when $tII = 1$; X is as above defined;

Y' is as Y above defined, but with three free valences instead of two, preferably it is selected from the following:

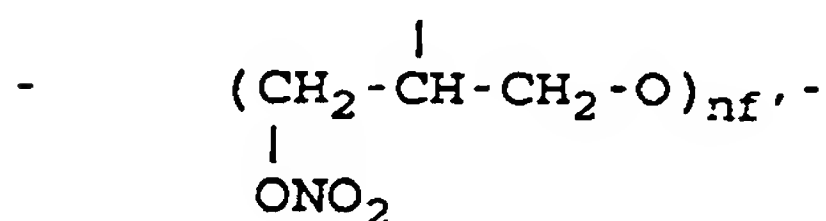
- a $-R'O-$ group wherein R' is linear or branched C_1C_{20} , preferably having from 1 to 6 carbon atoms, most preferably 2-4, or a saturated, optionally substituted, ring having from 5 to 7 carbon atoms;
- or



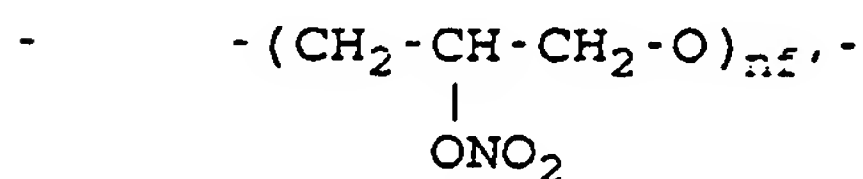
wherein n_3 is an integer from 0 to 3 and $n_{3'}$ is an integer from 1 to 3;



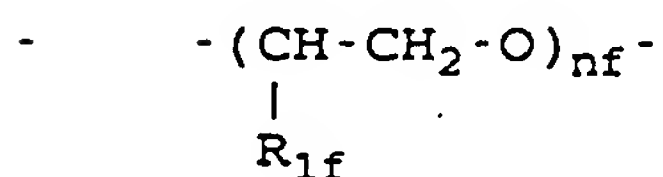
wherein n_3 and $n_{3'}$ have the above mentioned meaning;



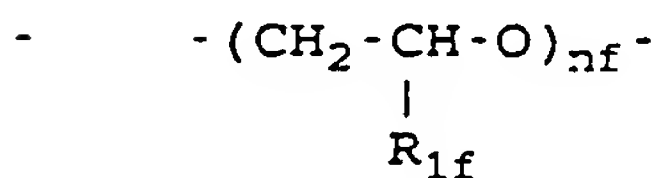
wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein n_f' is an integer from 1 to 6 preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;

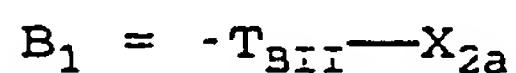


wherein $\text{R}_{1f} = \text{H}, \text{CH}_3$ and n_f is an integer from 1 to 6; preferably from 1 to 4; wherein one hydrogen atom

on one of the carbon atoms is substituted by a free valence;

preferably $Y' = -R'O-$ wherein R' is a linear or branched C_2-C_4 , the oxygen which in Y' is covalently linked to the $-N(O)_s$ group is at the end of the free bond indicated in C_1 formula;

or $Y' = Y_0$ as defined in (I) but with three free valences instead of 2;



wherein X_{2a} is a monovalent radical,

$T_{BII} = (CO)$ when $tI = 0$, $T_{BII} = X$ when $tII = 0$, X being as above defined;

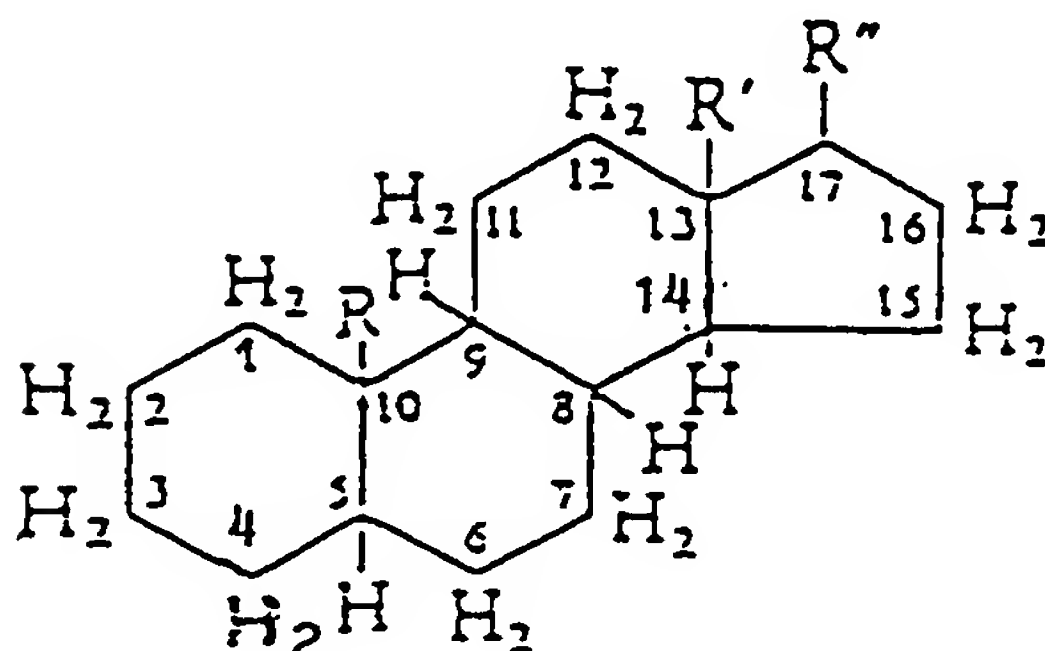
- X_2 , bivalent radical, is such that the corresponding precursor of B: $-T_3 - X_2 - T_{3i}$ meets test 4 or test 5, precursor in which the T_3 and T_{3i} free valences are each saturated with OZ, with Z or with $-Z^I-N-Z^{II}$, Z^I and Z^{II} being equal or different and have the Z values as above defined; depending on whether T_3 and/or $T_{3i} = CO$ or X, in connection with the values of t, t', tx and txx;

- the C precursor when $b0 = 0$ is of $-T_c-Y-H$ type wherein the T_c free valence is saturated with OZ, Z, or with $-Z^I-N-Z^{II}$, Z^I and Z^{II} being as above defined and is such as to meet test 5;

- X_{2a} monovalent radical, such that the corresponding

precursor of $B_1 - T_{BII} - X_{2a}$ meets test 4 or test 5,
 precursor wherein the T_{BII} free valence is saturated
 with OZ or with Z or with $-Z^I-N-Z^{II}$, Z^I and Z^{II}
 being equal or different and having the Z values as
 above defined, depending on whether $T_{BII} = CO$ or X,
 in connection with the tI and tII values;

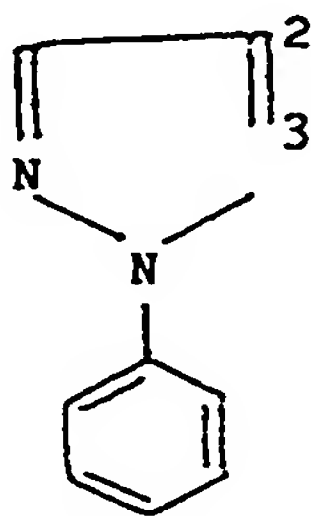
A = R-, has the following structure:



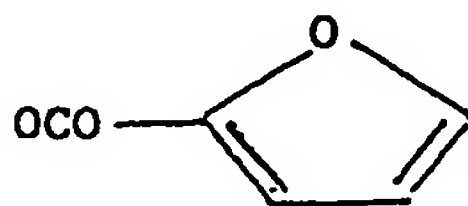
wherein in substitution of the hydrogens of the CH groups or of
 the two hydrogens of the CH₂ groups mentioned in the general
 formula, the following substituents can be present:

in position 1-2: there may be a double bond;

in position 2-3: there may be the following substituent:

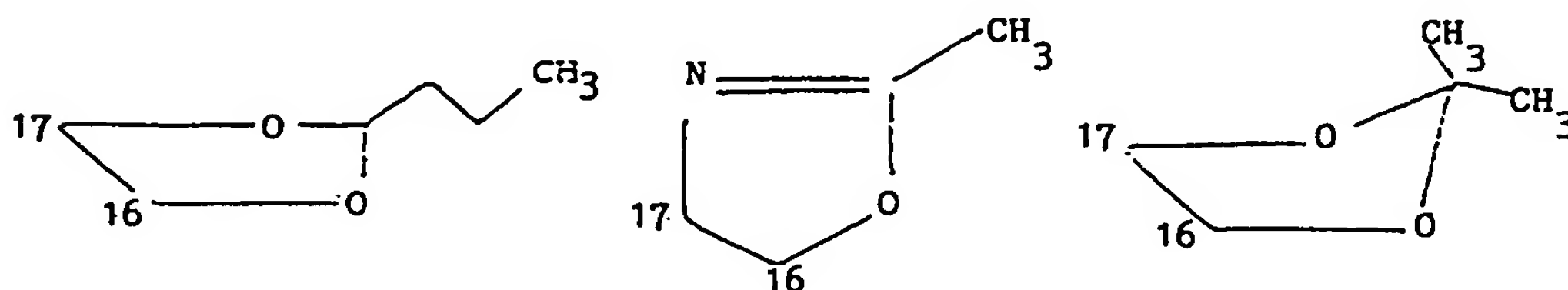


in position 2: there may be Cl, Br;
 in position 3: there may be CO, -O-CH₂-CH₂-Cl, OH;
 in position 3-4: there may be a double bond;
 in position 4-5: there may be a double bond;
 in position 5-6: there may be a double bond;
 in position 5-10: there may be a double bond;
 in position 6: there may be Cl, F, CH₃, -CHO;
 in position 7: there may be Cl, OH;
 in position 9: there may be Cl, F;
 in position 11: there may be OH, CO, Cl, CH₃;
 in position 16: there may be CH₃, OH, =CH₂;
 in position 17: there may be OH, CH₃, OCO(O)_{ua}(CH₂)_{va}CH₃, C≡CH
 or



wherein ua is an integer equal to 0 or 1, va is an integer from 0 to 4;

in position 16-17: there may be the following groups:



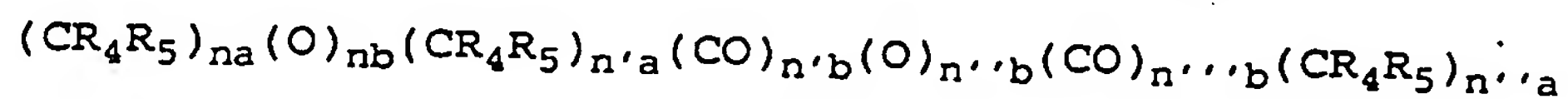
R and R', equal to or different from each other, can be hydrogen or linear or branched alkyls from 1 to 4 carbon atoms,

preferably $R = R' = CH_3$;

R'' is $-(CO-L)_t-(L)_{t2}-(X_0^I)_{t1}-$

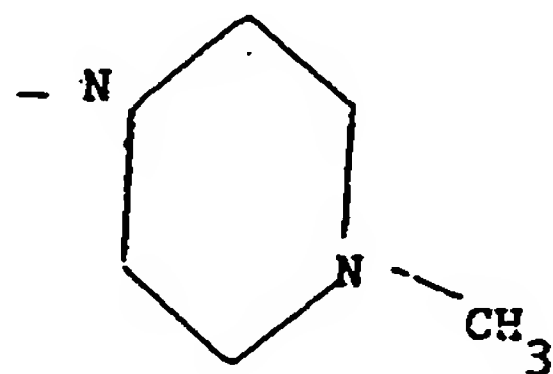
wherein t , $t1$ and $t2$ are integers equal to or different from each other, equal to 0 or 1, with the proviso that when $t = 0$ $t2 = 1$ and when $t = 1$ $t2 = 0$, and that t and $t1$, or $t2$ and $t1$, cannot contemporaneously be equal to 0 when A does not contain -OH groups;

the bivalent bridging group L is selected from:



wherein na , $n'a$, and $n''a$, equal to or different from each other, are integers from 0 to 6, preferably 1-3; nb , $n'b$, $n''b$ and $n''''b$, equal to or different from each other, are integers equal to 0 or 1; R_4 , R_5 , equal to or different from each other, are selected from H, linear or branched alkyl from 1 to 5 carbon atoms, preferably from 1 to 3;

X_0^I is X as above defined, but R_{1c} is a linear or branched alkyl from 1 to 10 carbon atoms, or equal to X_2^I wherein X_2^I is equal to OH, CH_3 , Cl, $N(-CH_2-CH_3)_2$, SCH_2F , SH, or



wherein test 4 is the following: it is an analytical determination carried out by adding portions of methanol

solutions of the precursor of B or B₁ at a 10⁻⁴ M concentration, to a methanol solution of DPPH (2,2-diphenyl-1-picryl hydrazyl - free radical); after having maintained the solution at room temperature away from light for 30 minutes, it is read the absorbance at the wave length of 517 nm of the test solution and of a solution containing only DPPH in the same amount as in the test solution; and then the inhibition induced by the precursor towards radical production by DPPH is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the test compound + DPPH and that of the solution containing only DPPH; the acceptance criterium of the compounds according to this test is the following: test 4 is met by B or B₁ precursor compounds if the inhibition percentage as above defined is higher than or equal to 50%;

wherein test 5 is the following: it is an analytical determination carried out by adding aliquots of 10⁻⁴ M methanol solutions of the precursor of B or B₁ or of C = -T_C-Y-H, having the free valence saturated as above indicated, to a solution formed by admixing a 2 mM solution of desoxyribose in water with 100 mM of phosphate buffer and 1 mM of the salt Fe^{II}(NH₄)₂(SO₄)₂; after having thermostatted the solution at 37°C for one hour, aliquots of aqueous solutions of trichloroacetic acid 2.8% and of thiobarbituric acid 0.5 M are

added, in the order, heating is effected at 100°C for 15 minutes and the absorbance of the tested solutions is then read at 532 nm; the inhibition induced by the precursor of B or B₁ or C = -T_C-Y-H with respect to radical production by Fe^{II} is calculated as a percentage by means of the following formula:

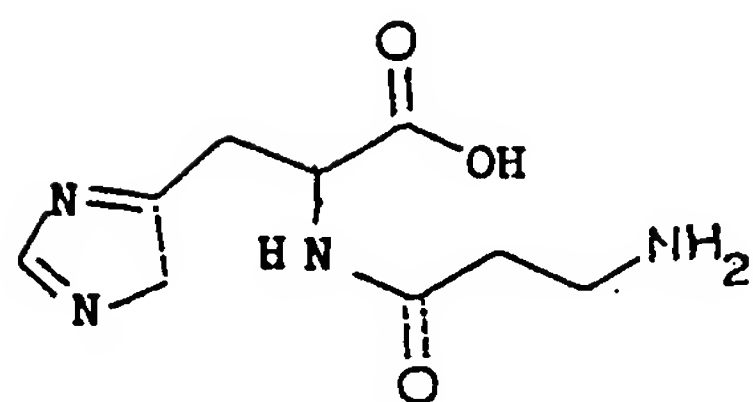
$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound and the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage as above defined of the precursor of B or B₁ or C = -T_C-Y-H, having the free valence saturated as above indicated, is higher than or equal to 50%; provided that in the compounds of formula (I) are excluded the drugs with A = R-, wherein R is as above defined, when b₀ = 0 and C = -T_C-Y₀- wherein the free valence of Y₀ is saturated as indicated above, s = 1 or 2.

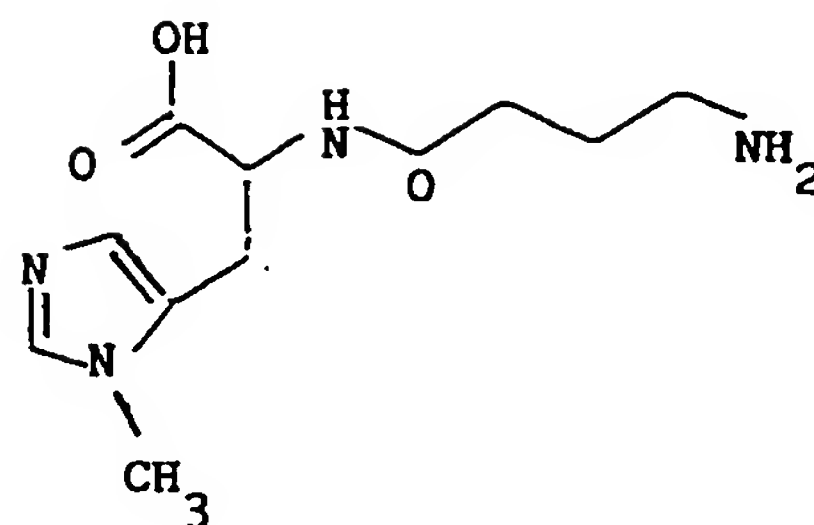
Preferably the B or B₁ precursor compound (precursor of the X₂ or X_{2a} radical in formulas (I) and (II) respectively) which meets test 4, is selected from the following classes of compounds:

- Aminoacids, selected from the following: L-carnosine (formula CI), anserine (CII), selenocysteine (CIII), selenomethionine (CIV), penicillamine (CV), N-acetylpenicillamine (CVI), cysteine (CVII), N-acetylcysteine (CVIII), glutathione (CIX) or its esters, preferably ethyl

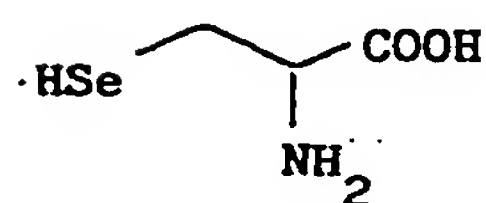
or isopropyl ester:



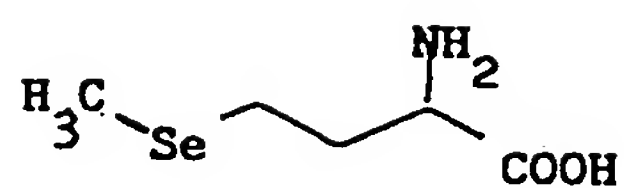
(CI)



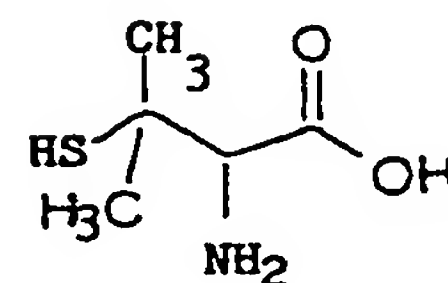
(CII)



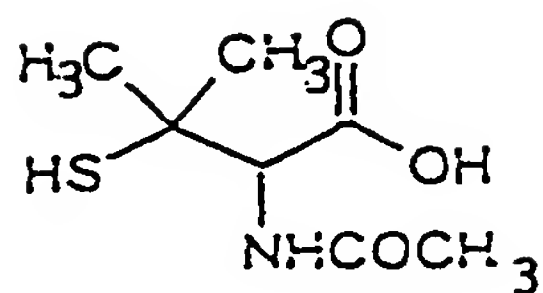
(CIII)



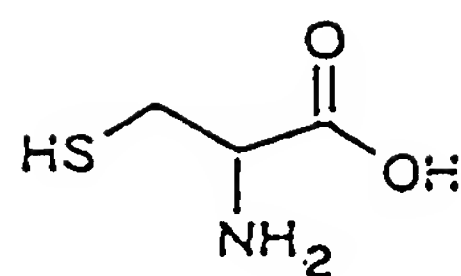
(CIV)



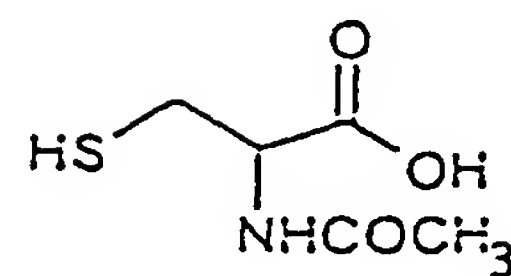
(CV)



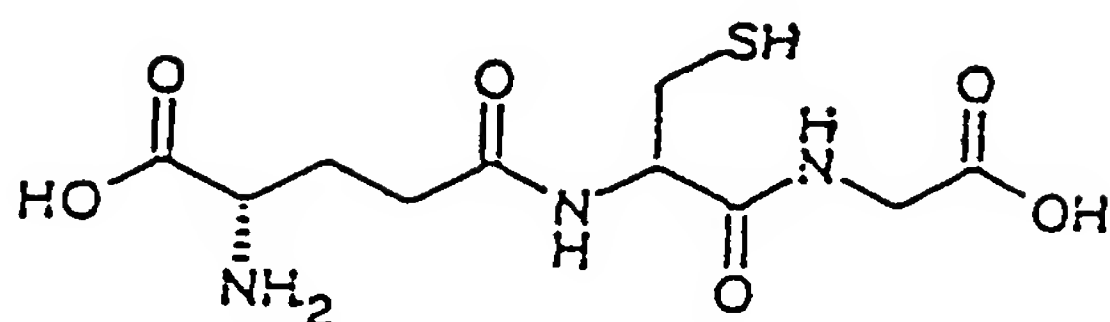
(CVI)



(CVII)



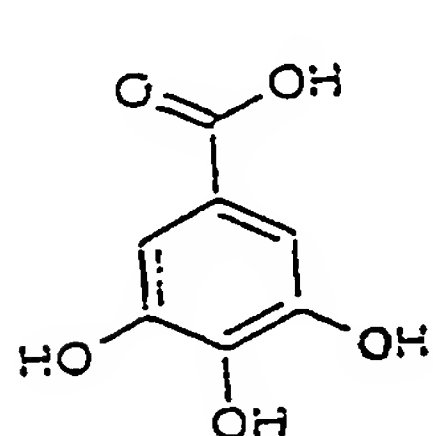
(CVIII)



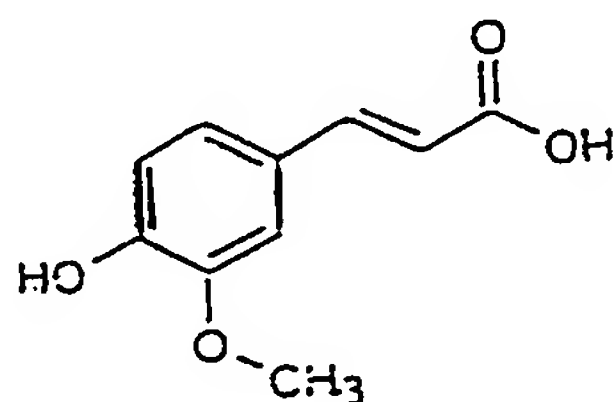
(CIX)

- hydroxyacids, selected from the following: gallic acid

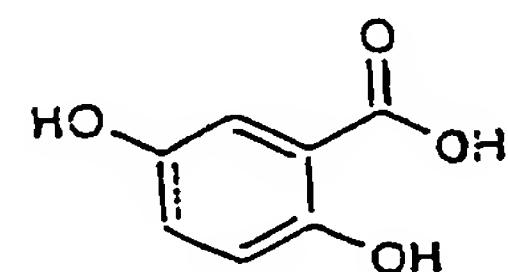
(formula DI), ferulic acid (DII), gentisic acid (DIII), citric acid (DIV), caffeic acid (DV), hydrocaffeic acid (DVI), p-coumaric acid (DVII), vanillic acid (DVIII), chlorogenic acid (DIX), kynurenic acid (DX), syringic acid (DXI):



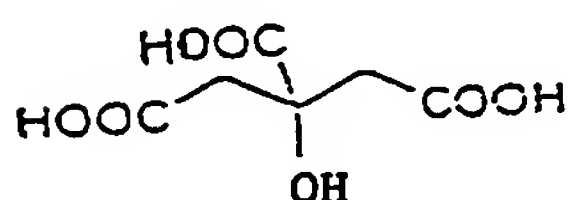
(DI)



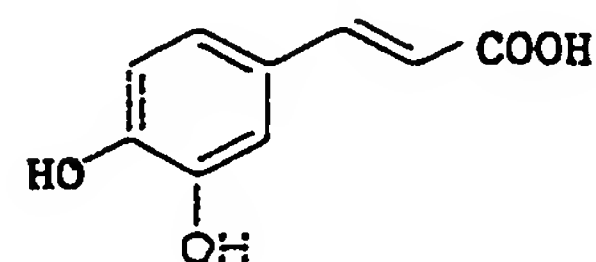
(DII)



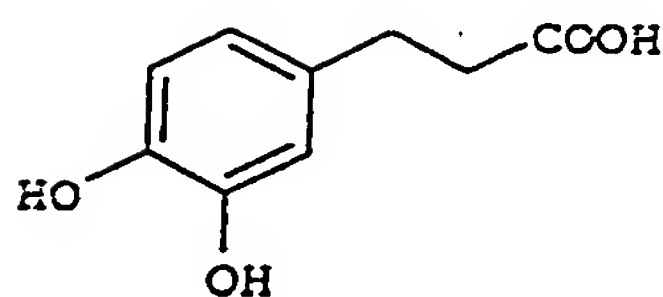
(DIII)



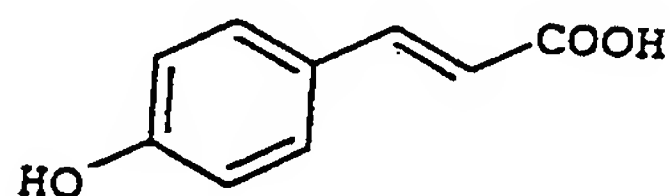
(DIV)



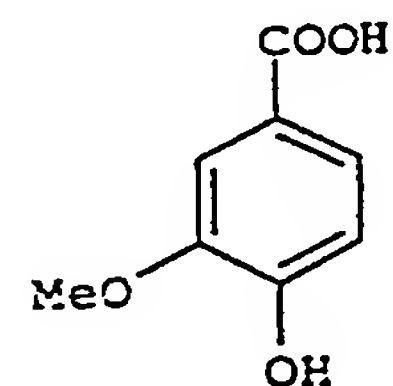
(DV)



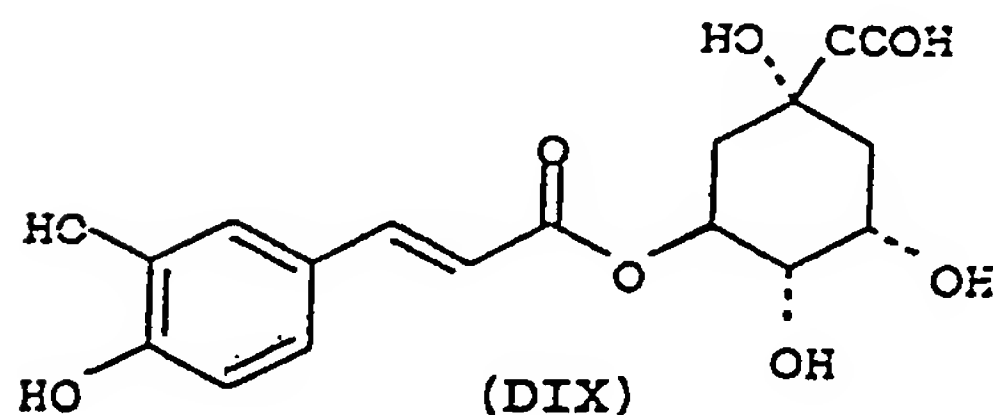
(DVI)



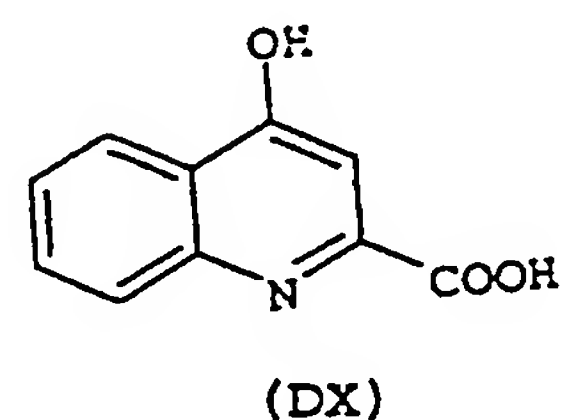
(DVII)



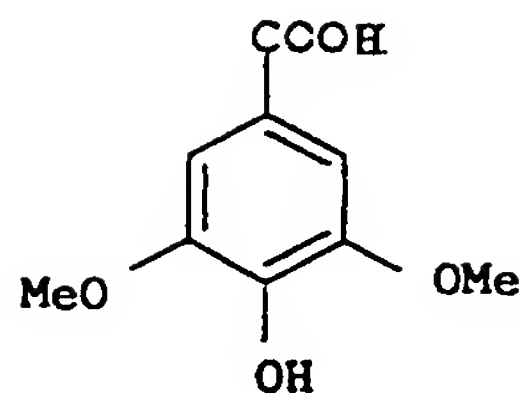
(DVIII)



(DIX)

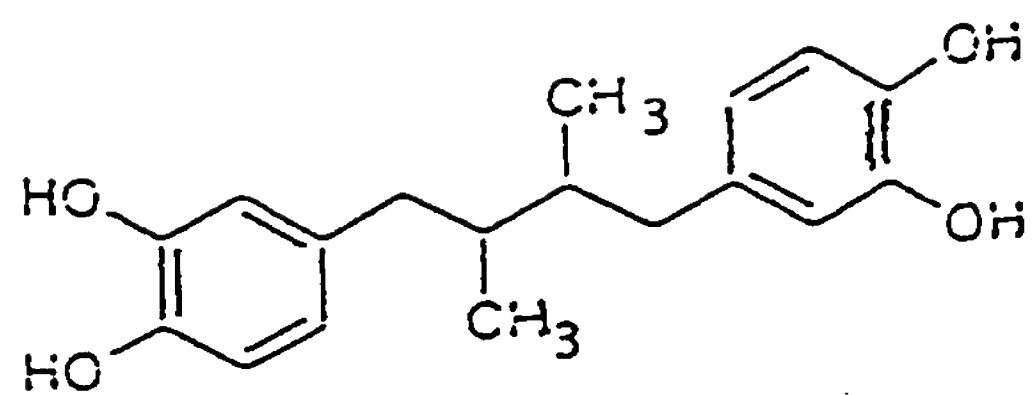


(DX)

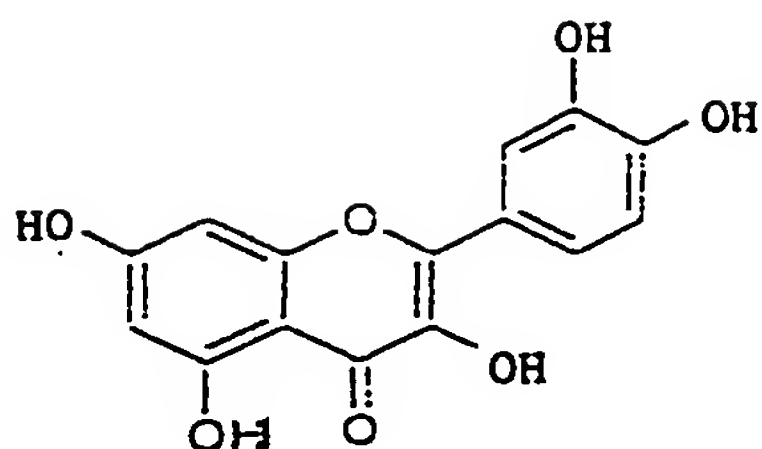


(DXI)

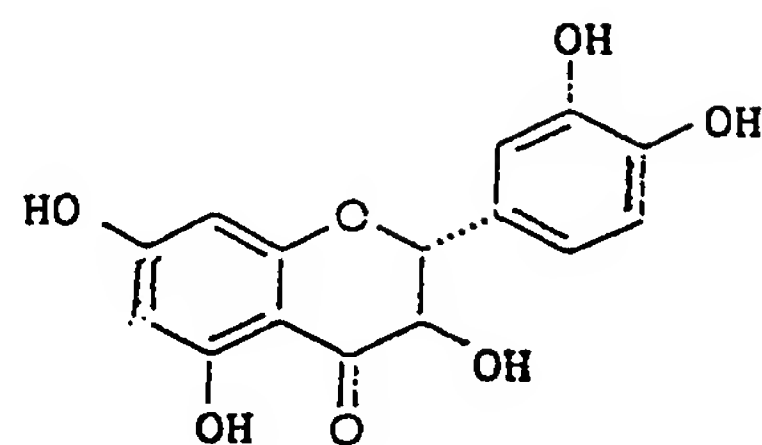
- Aromatic and heterocyclic mono- and polyalcohols, selected from the following: nordihydroguaiaretic acid (EI), quercetin (EII), catechin (EIII), kaempferol (EIV), sulphurethyne (EV), ascorbic acid (EVI), isoascorbic acid (EVII), hydroquinone (EVIII), gossypol (EIX), reductic acid (EX), methoxyhydroquinone (EXI), hydroxyhydroquinone (EXII), propyl gallate (EXIII), saccharose (EXIV), vitamin E (EXV), vitamin A (EXVI), 8-quinolol (EXVII), 3-tert-butyl-4-hydroxyanisole (EXVIII), 3-hydroxyflavone (EXIX), 3,5-tert-butyl-p-hydroxytoluene (EXX), p-tert-butyl phenol (EXXI), timolol (EXXII), xibornol (EXXIII), 3,5-di-ter-butyl-4-hydroxybenzyl-thioglycolate (EXXIV), 4'-hydroxybutyranilide (EXXV), guaiacol (EXXVI), tocol (EXXVII), isoeugenol (EXXVIII), eugenol (EXXIX), piperonyl alcohol (EXXX), allopurinol (EXXXI), conyferyl alcohol (EXXXII), 4-hydroxyphenetyl alcohol (EXXXIII), p-coumaric alcohol (EXXXIV), curcumin (EXXXV):



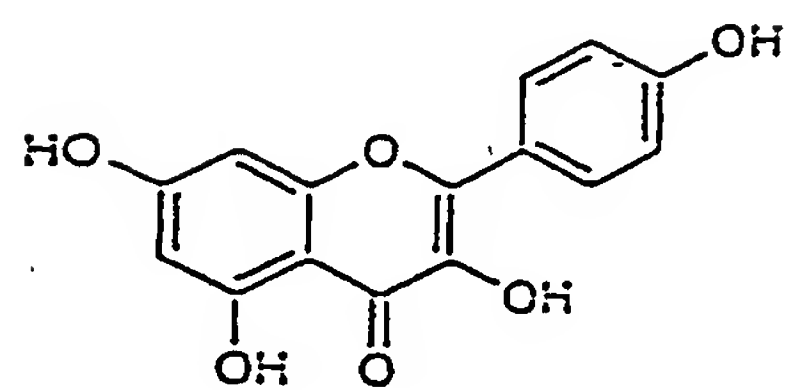
(EI)



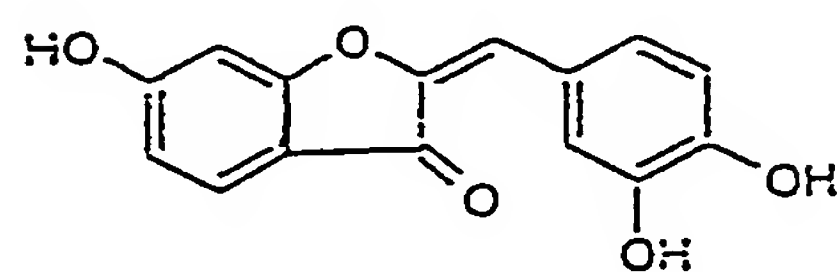
(EII)



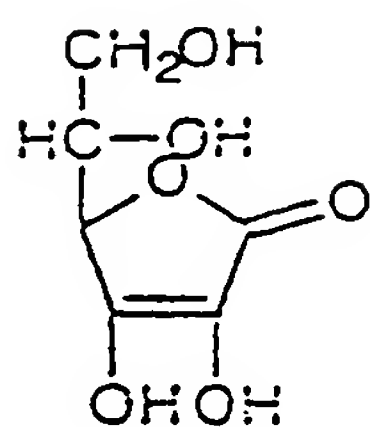
(EIII)



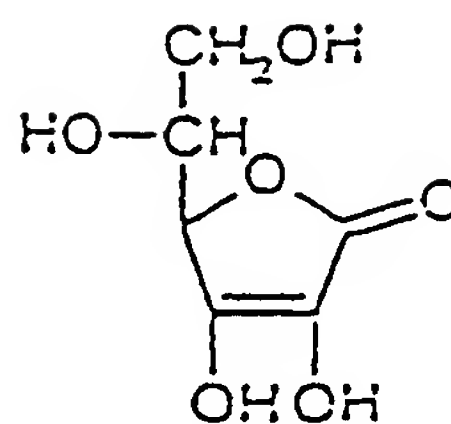
(EIV)



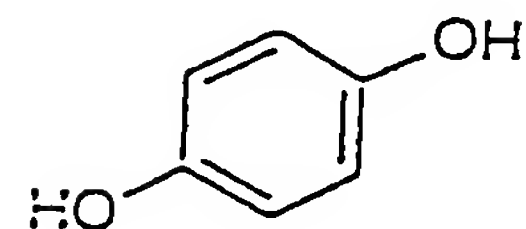
(EV)



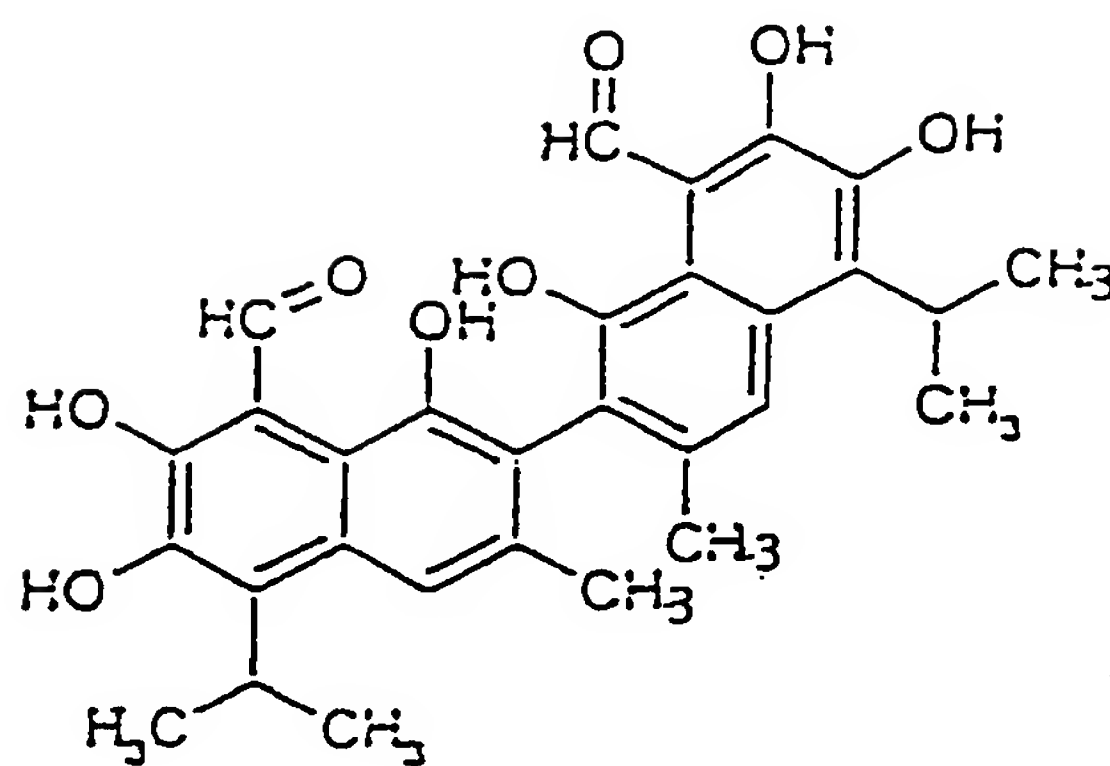
(EVI)



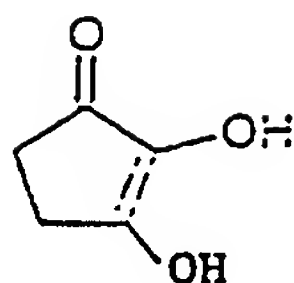
(EVII)



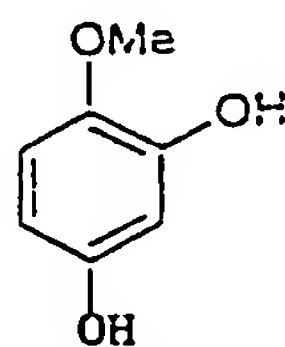
(EVIII)



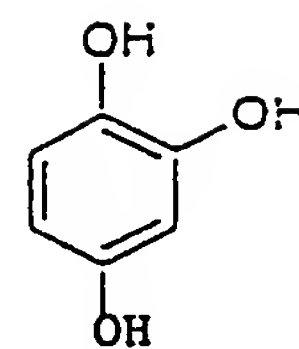
(EIX)



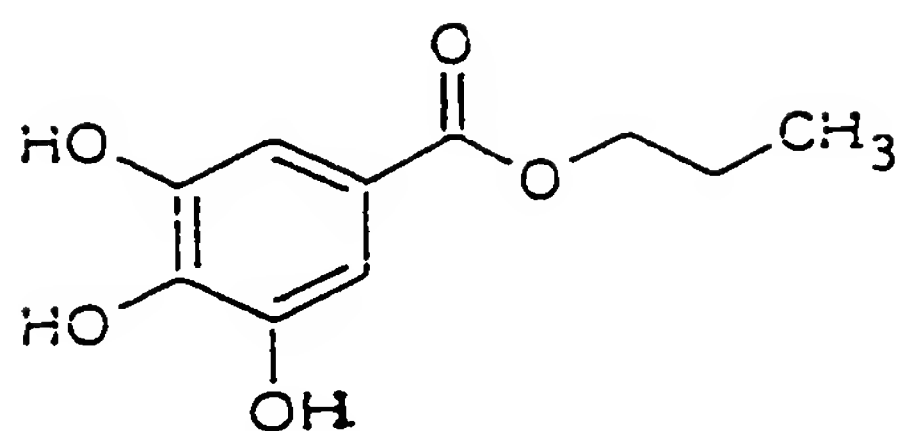
(EX)



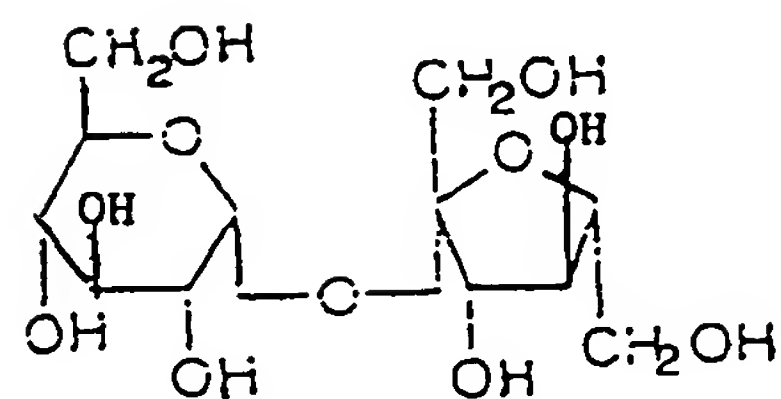
(EXI)



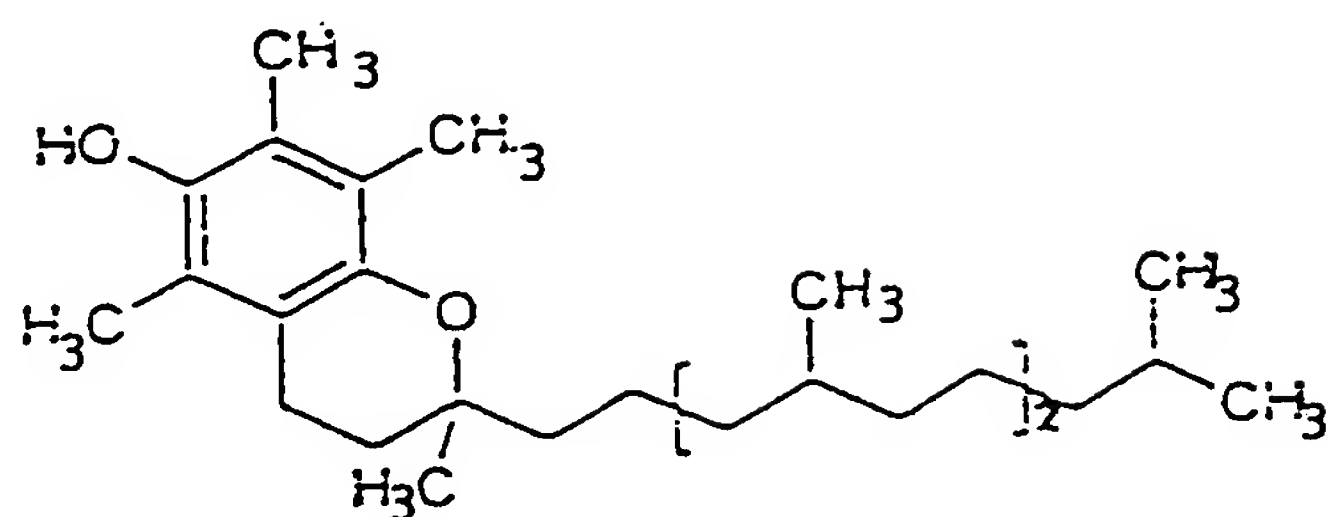
(EXII)



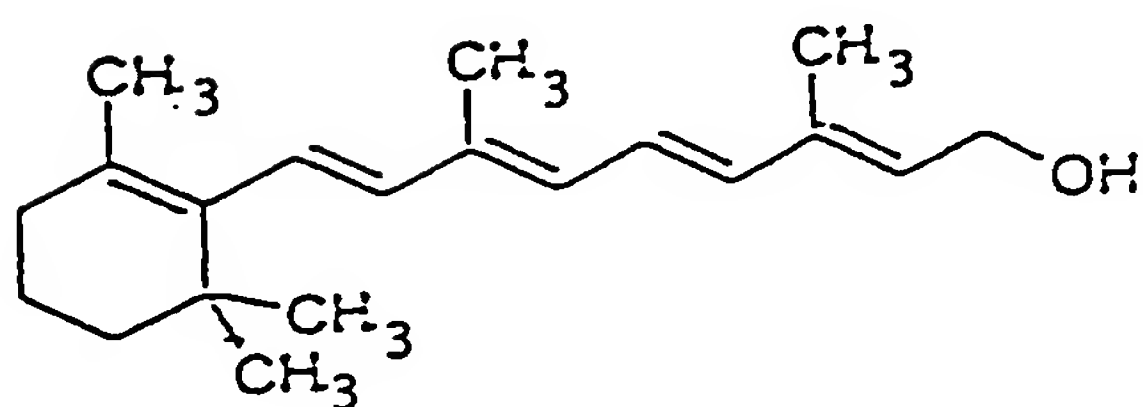
(EXIII)



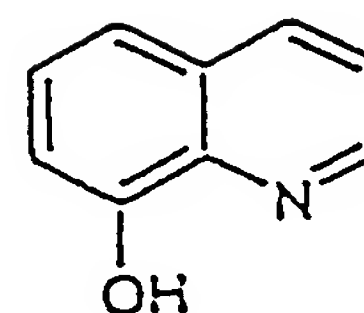
(EXIV)



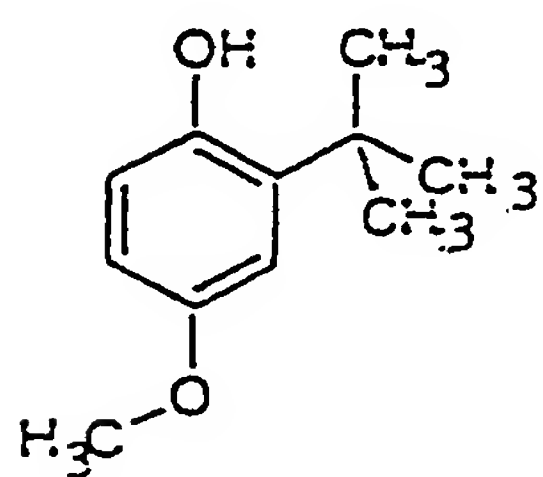
(EXV)



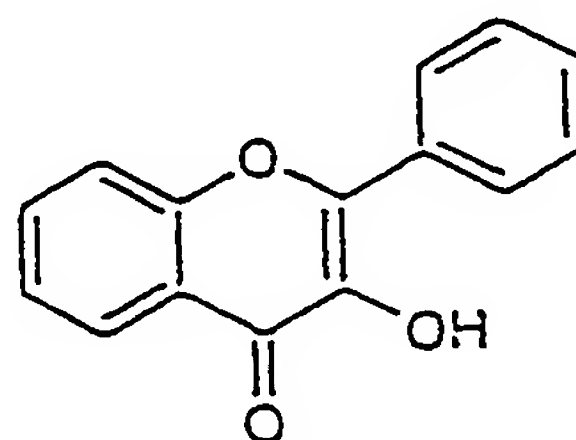
(EXVI)



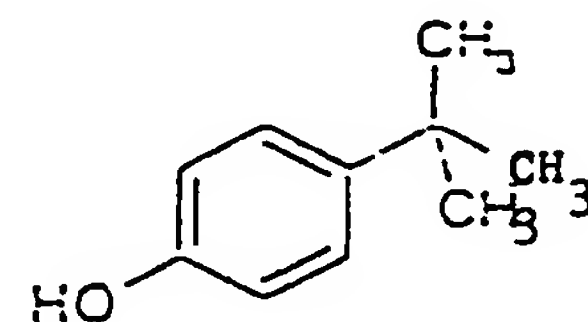
(EXVII)



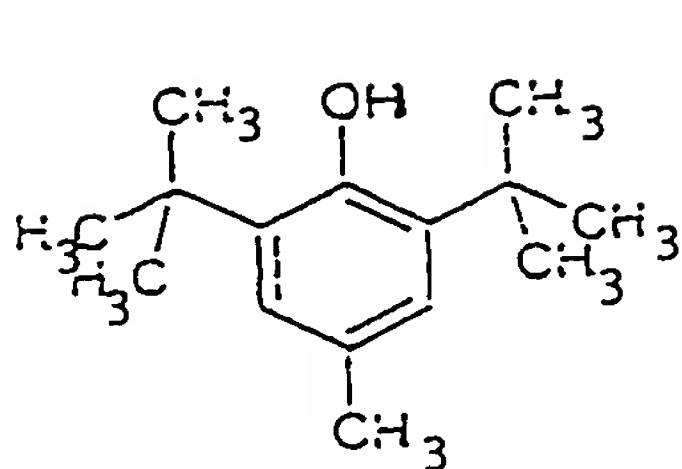
(EXVIII)



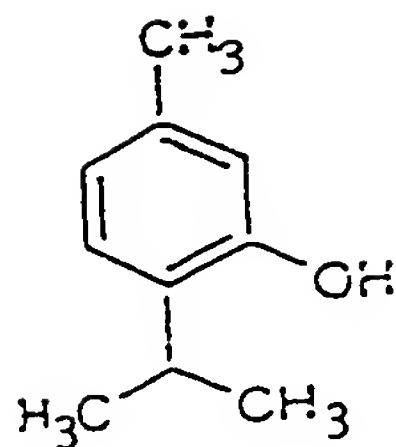
(EXIX)



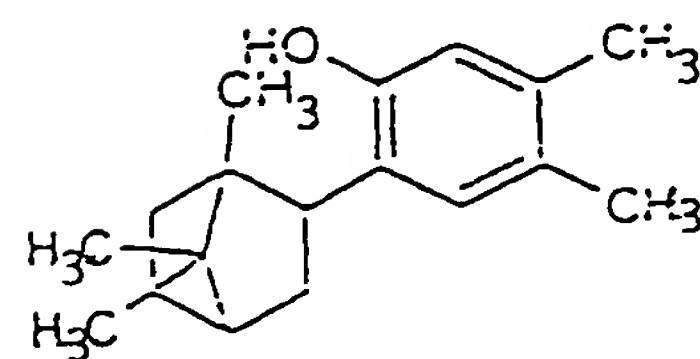
(EXXI)



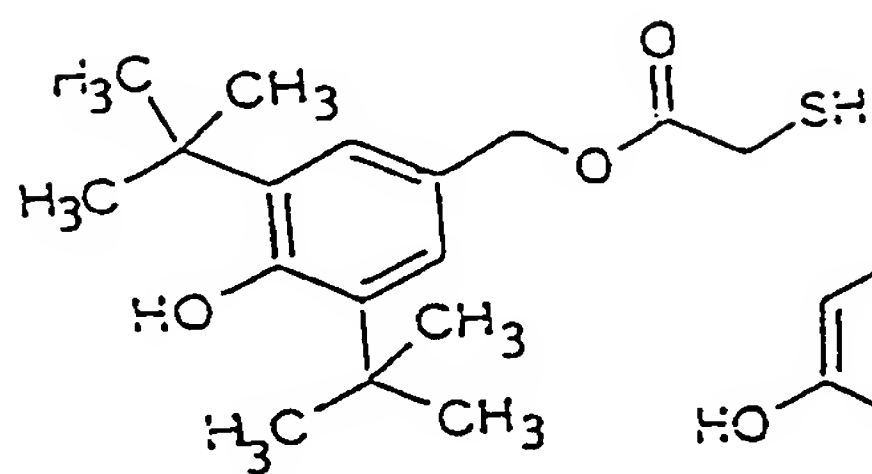
(EXX)



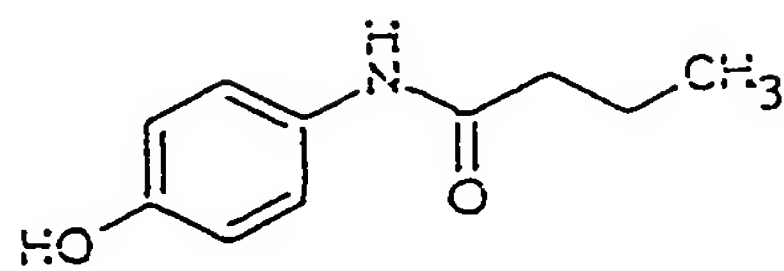
(EXXII)



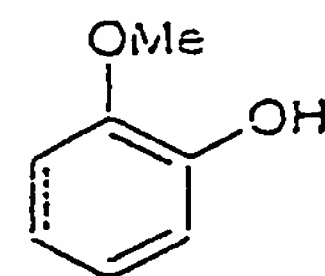
(EXXIII)



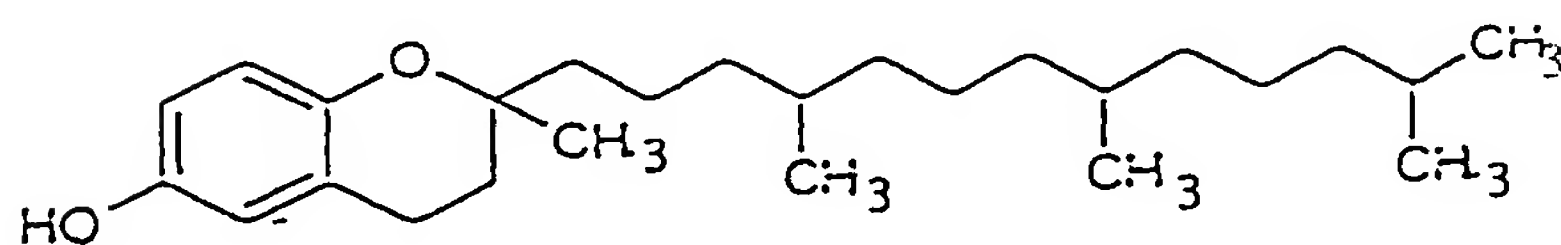
(EXXIV)



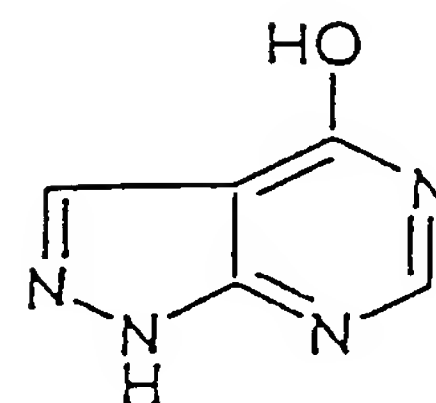
(EXXV)



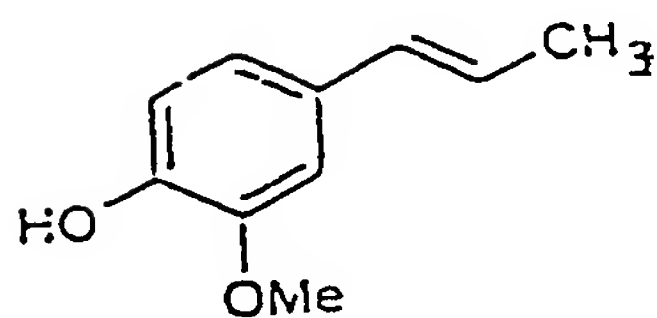
(EXXVI)



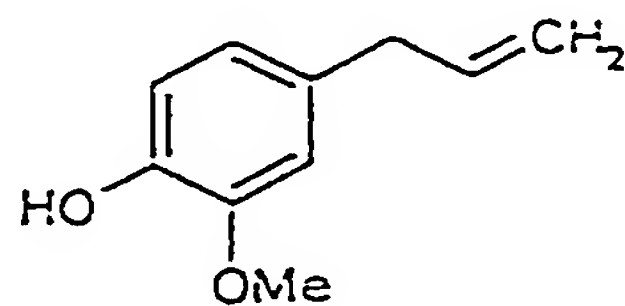
(EXXVII)



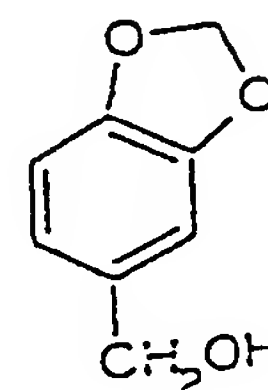
(EXXXI)



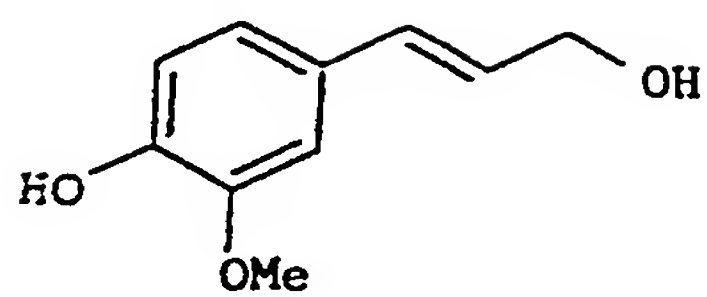
(EXXVIII)



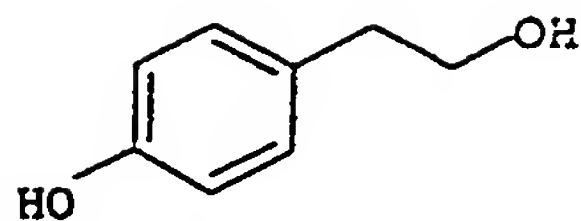
(EXXIX)



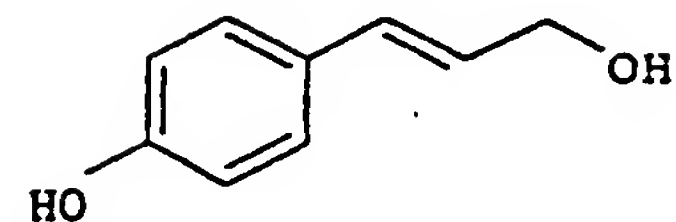
(EXXX)



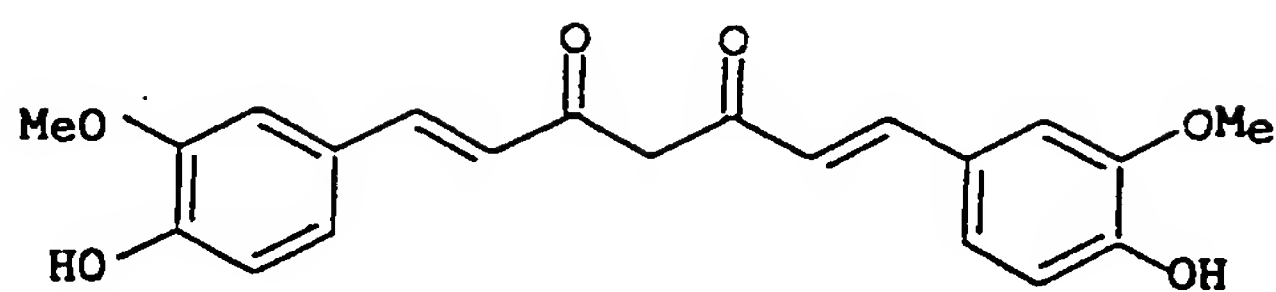
(EXXXII)



(EXXXIII)

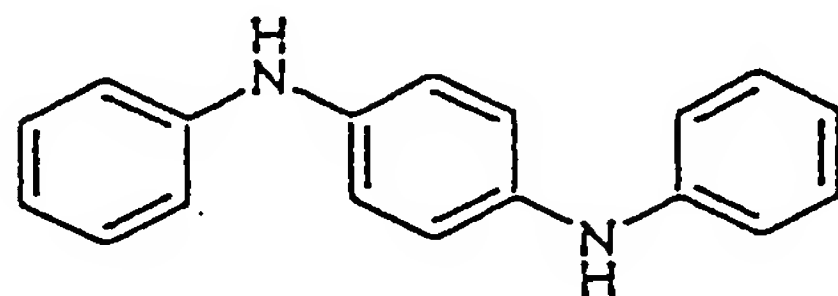


(EXXXIV)

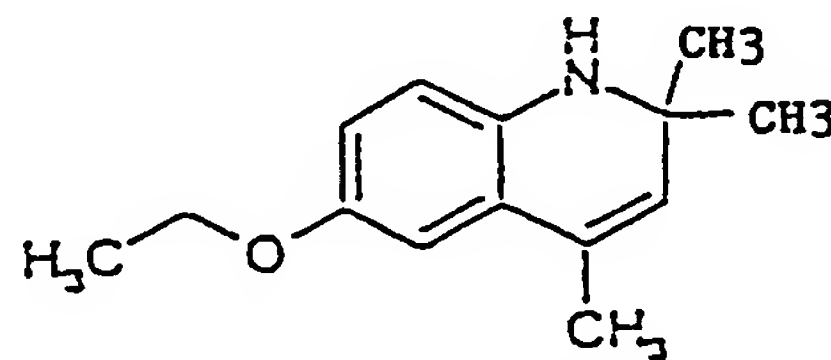


(EXXXV)

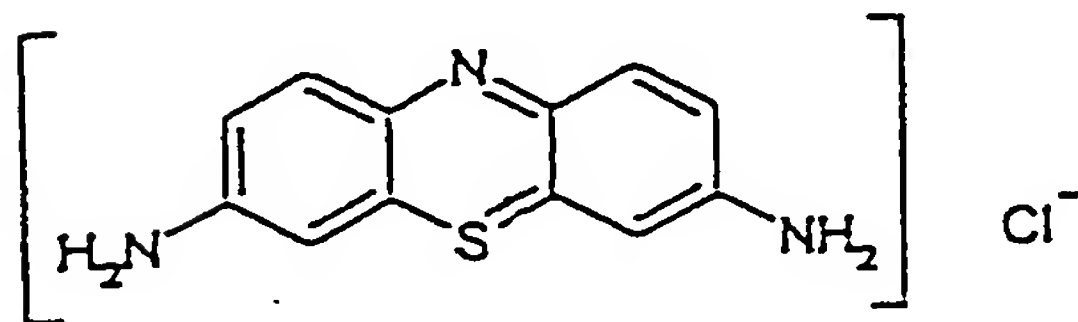
- aromatic and heterocyclic amines, selected from the following: N, N'-diphenyl-p-phenylenediamine (MI), ethoxyquin (MII), thionine (MIII), hydroxyurea (MIV):



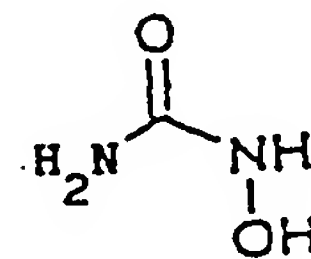
(MI)



(MII)

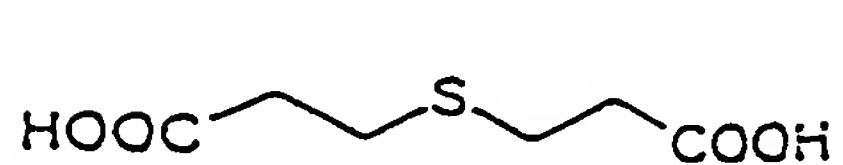


(MIII)

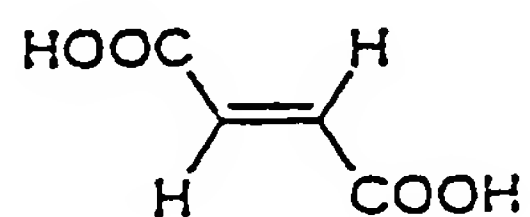


(MIV)

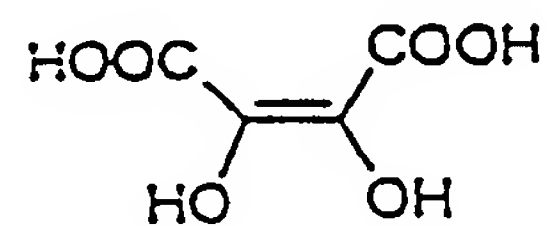
- Compounds containing at least a free acid function, selected from the following: 3,3'-thiodipropionic acid (NI), fumaric acid (NII), dihydroxymaleic acid (NIII), thiocctic acid (NIV), edetic acid (NV), bilirubin (NVI), 3,4-methylenedioxycinnamic acid (NVII), piperonylic acid (NVIII):



(NI)



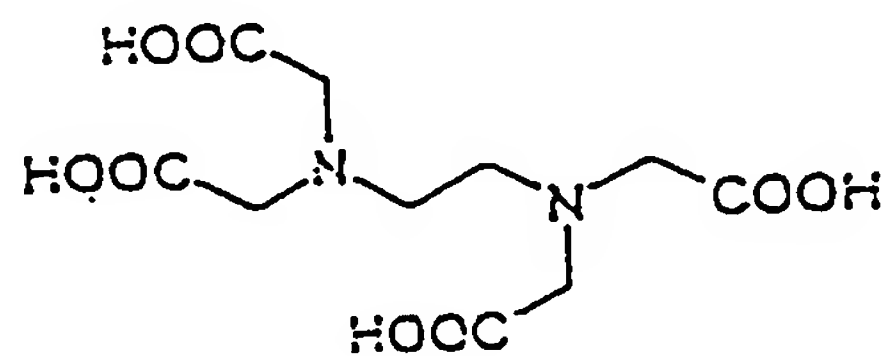
(NII)



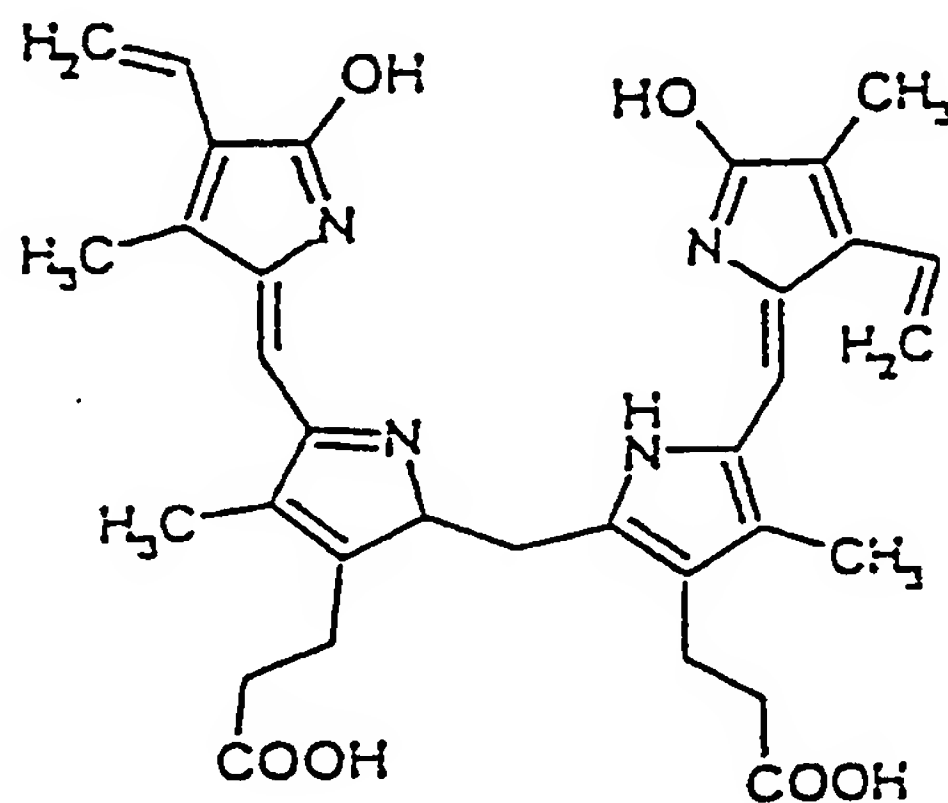
(NIII)



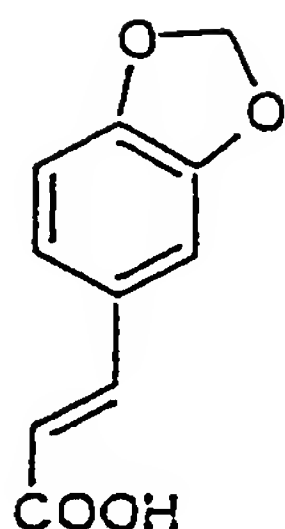
(NIV)



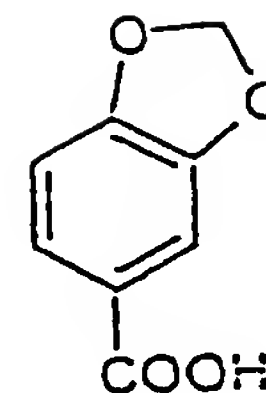
(NV)



(NVI)



(NVII)

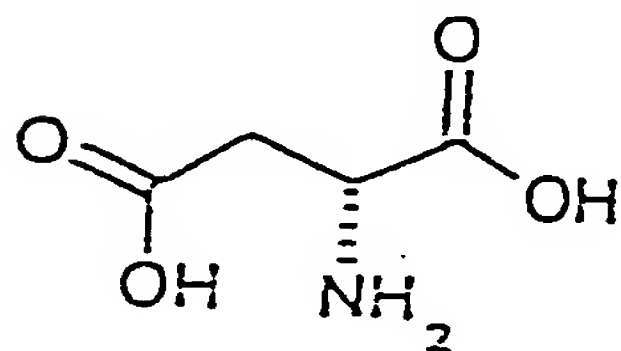


(NVIII)

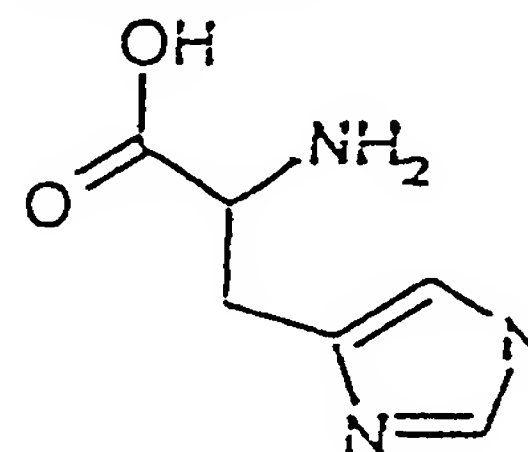
The above mentioned substances precursors of B or B₁ are prepared according to the known methods in the prior art, described, for example, in "The Merck Index, 12a Ed. (1996), herein incorporated by reference. When available, the corresponding isomers and optical isomers can be used.

Preferably the precursor compound of B or of B₁ (precursor of the X₂ or X_{2a} radical in formulas (I) and (II) respectively) which meets test 5, is selected from the following compounds:

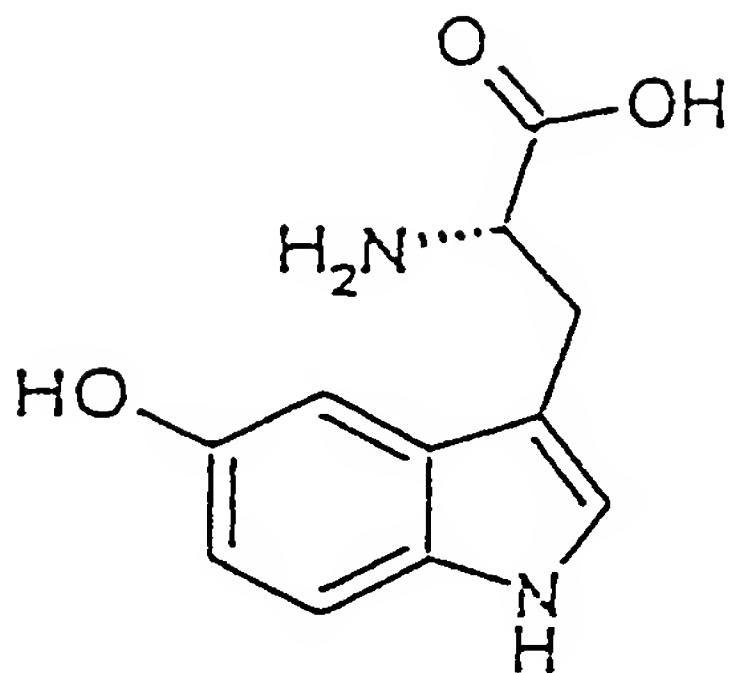
- Aminoacids: aspartic acid (PI), histidine (PII), 5-hydroxytryptophan (PIII), 4-thiazolidincarboxylic acid (PIV), 2-oxo-4-thiazolidincarboxylic acid (PV)



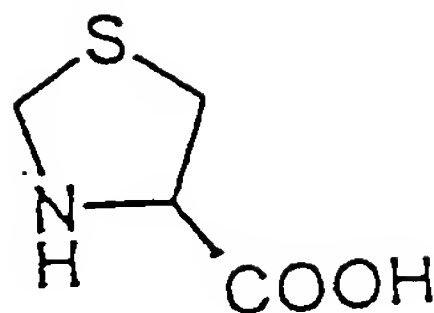
(PI)



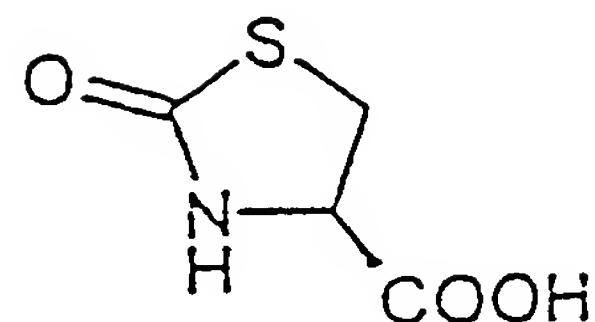
(PII)



(PIII)

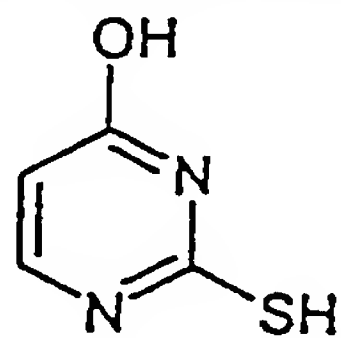


(PIV)



(PV)

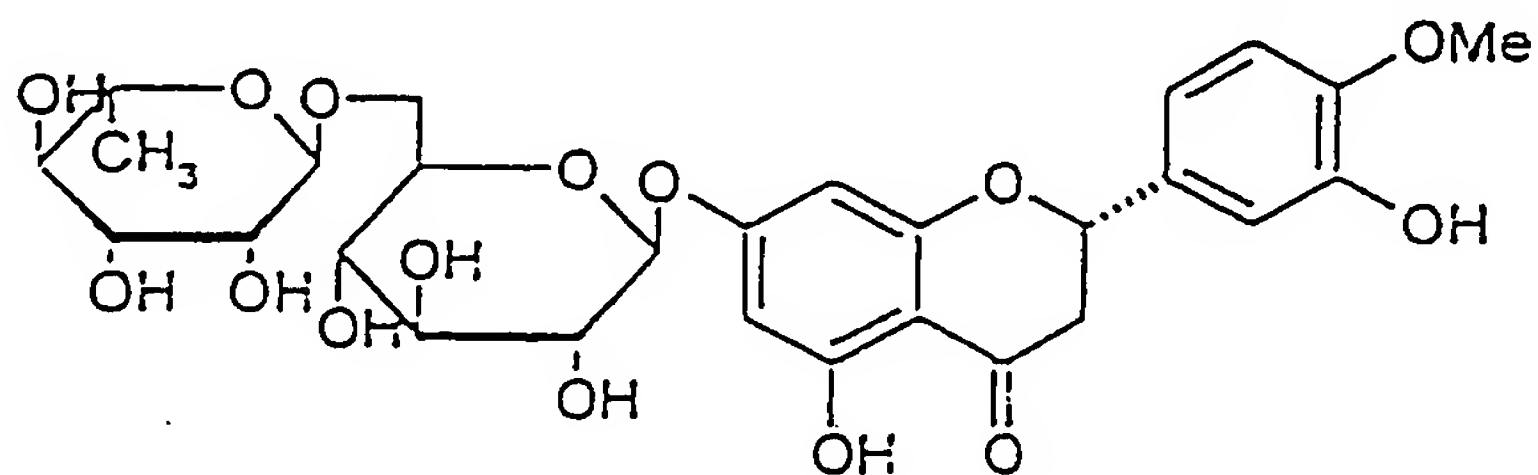
- mono and polyalcohols or thiols: 2-thiouracil (QI), 2-mercaptoethanol (QII), esperidine (QIII), secalciferol (QIV), 1- α -OH vitamin D2 (QV), flocalcitriol (QVI), 22-oxacalcitriol (QVII), the vitamin D3 derivative esterified with the vitamin A radical (QVIII), the formula (QIX) compound, 24,28-methylene-1 α -hydroxyvitamin D2 (QX) the compound derived from 1 α ,25-dihydroxyvitamin D2 (QXI), 2-mercaptoimidazol (QXII)



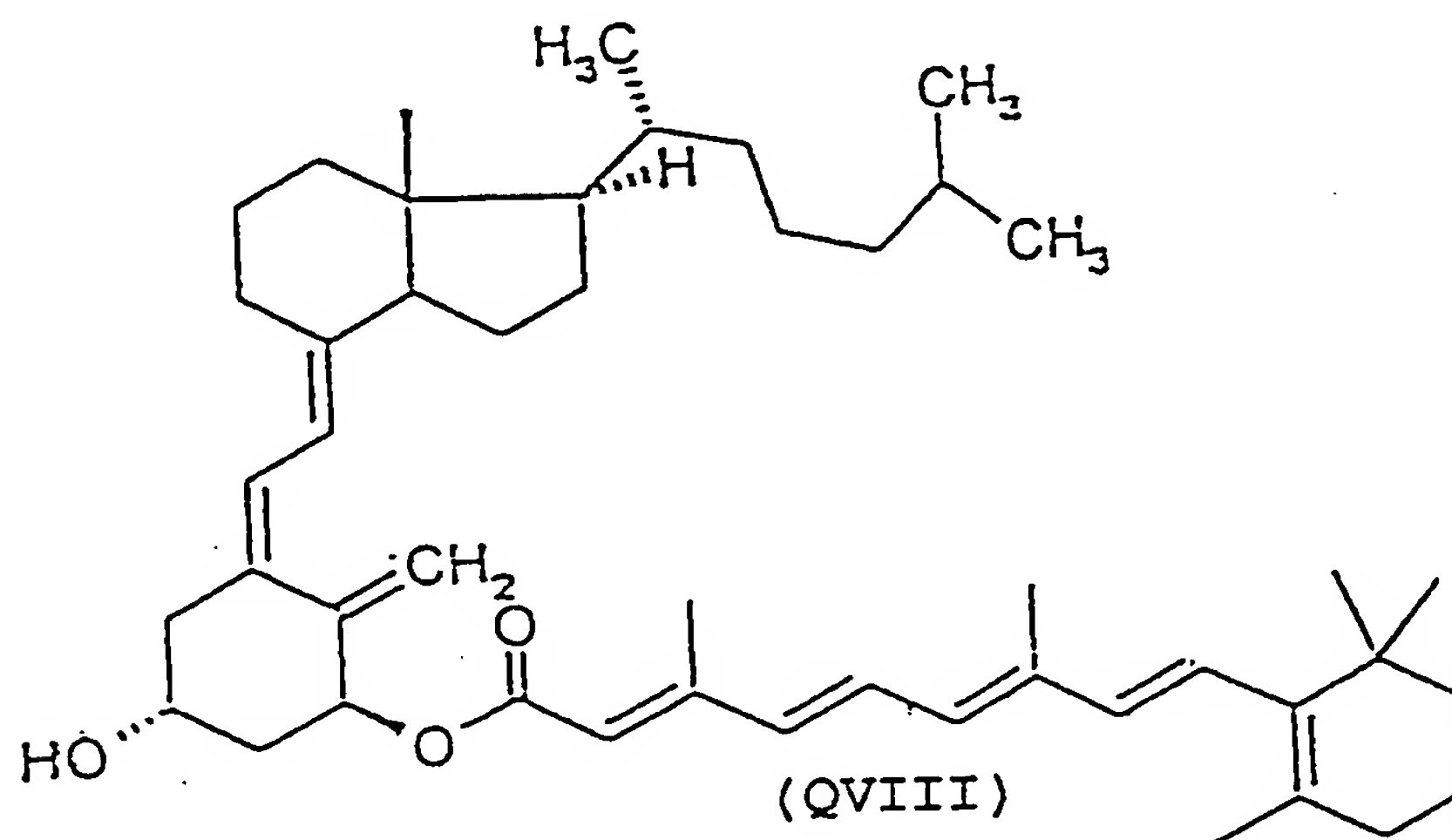
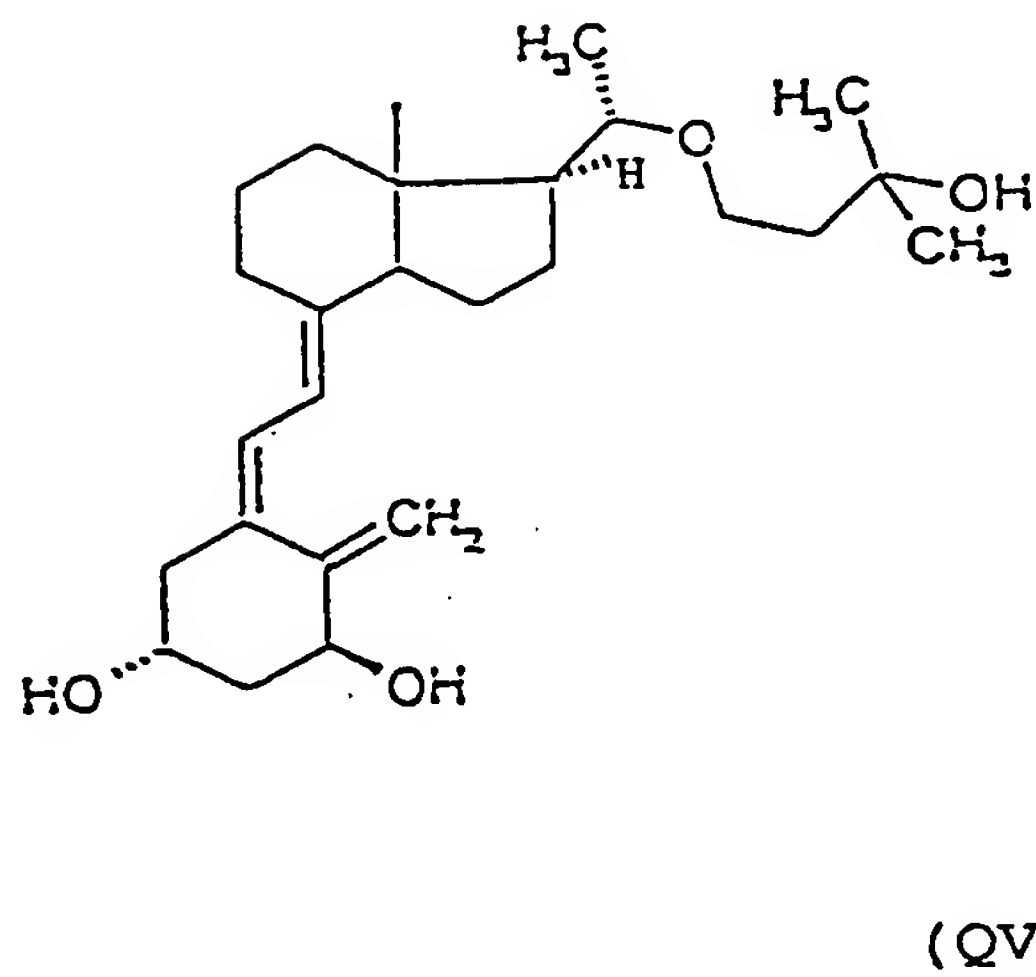
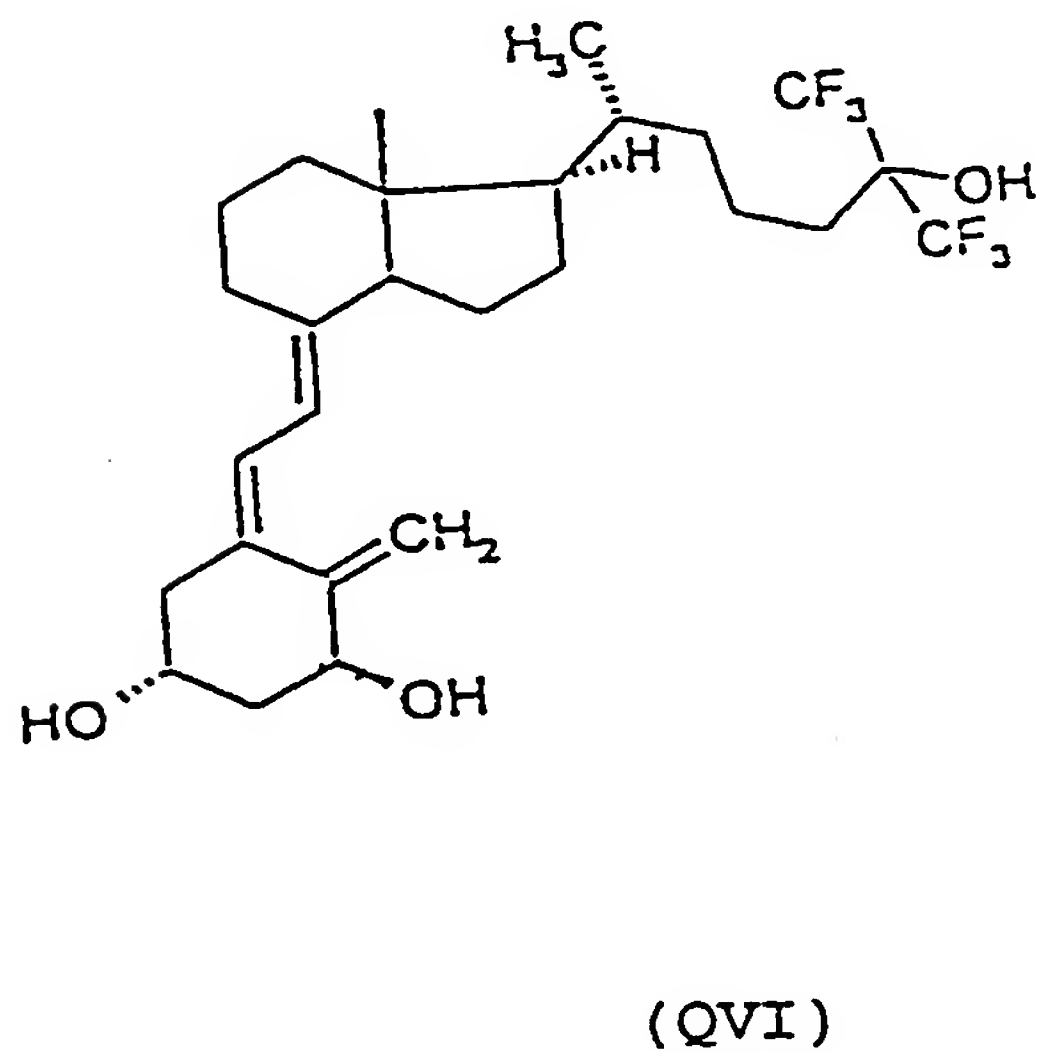
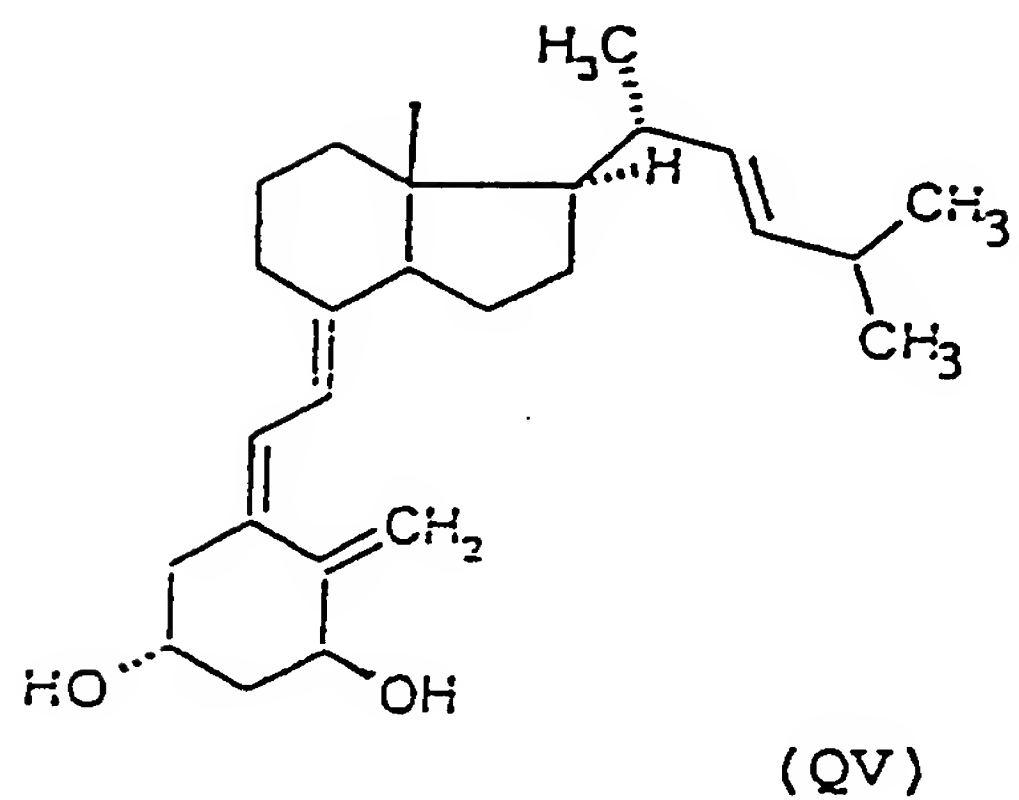
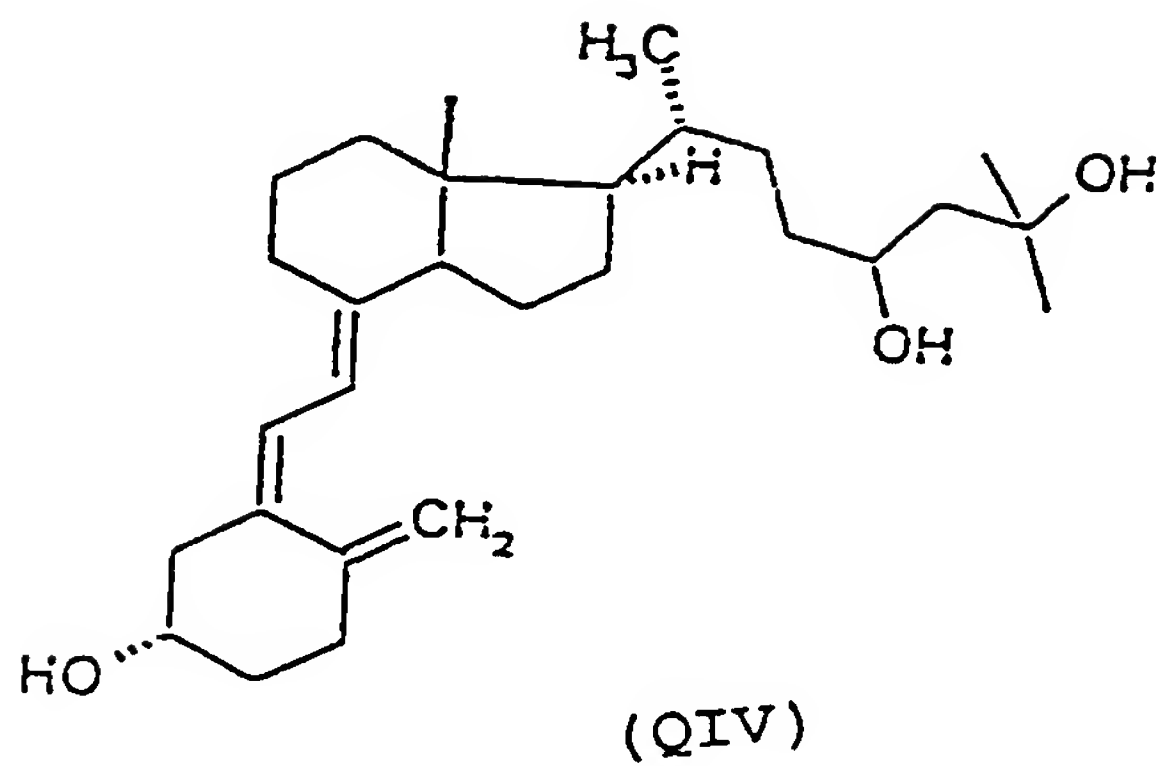
(QI)

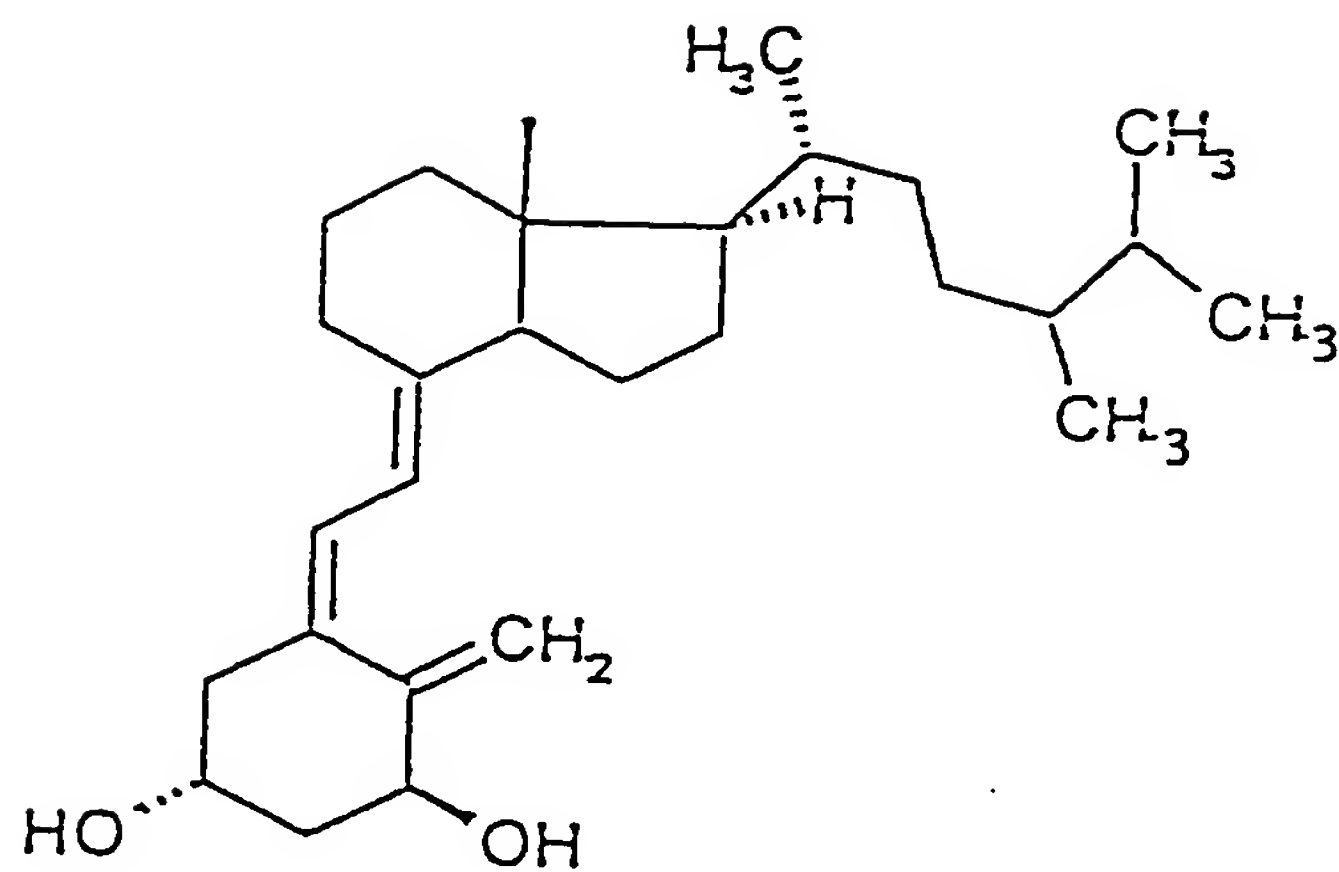


(QII)

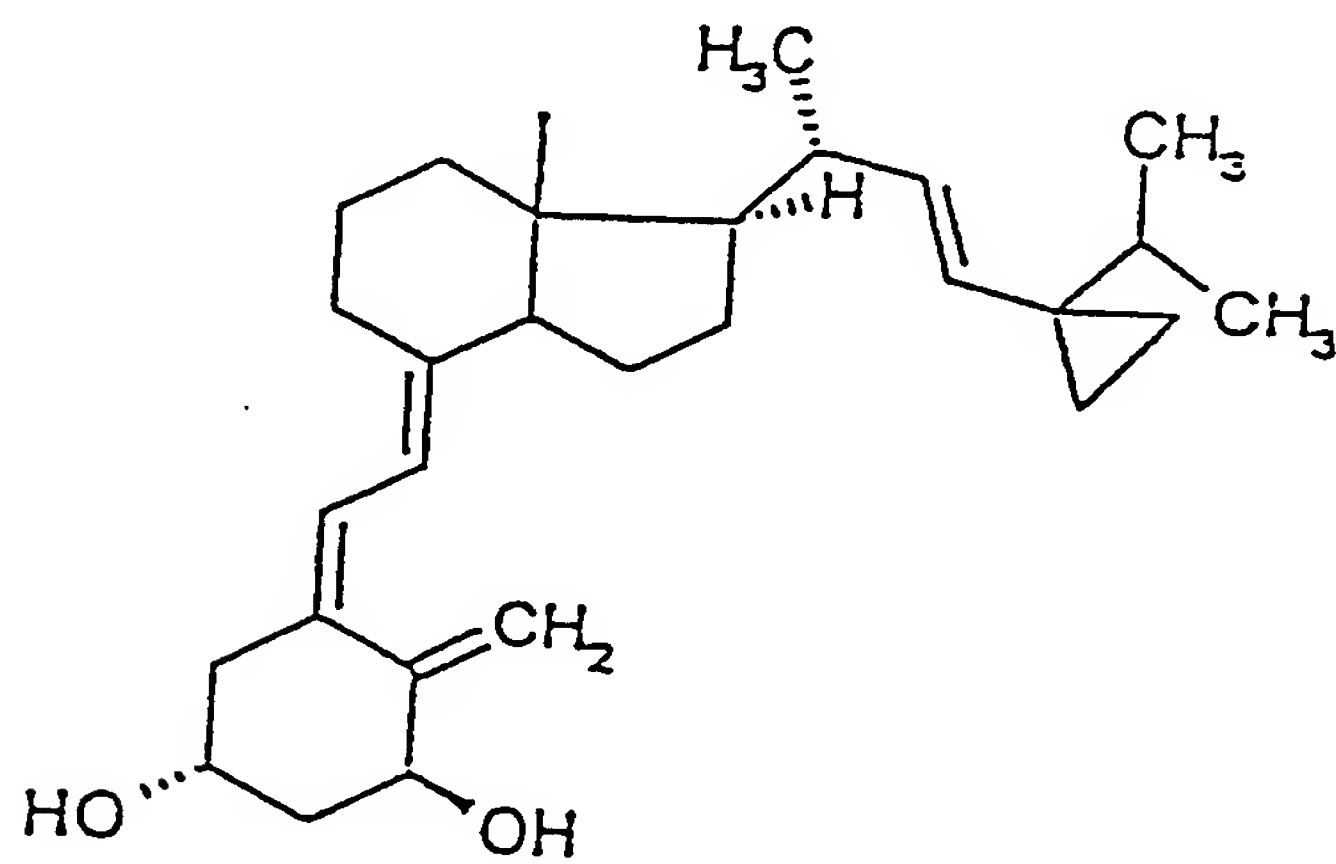


(QIII)

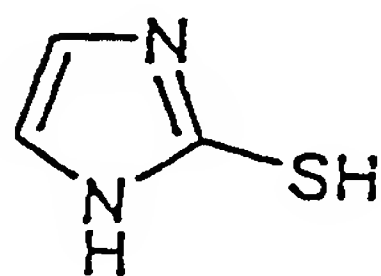




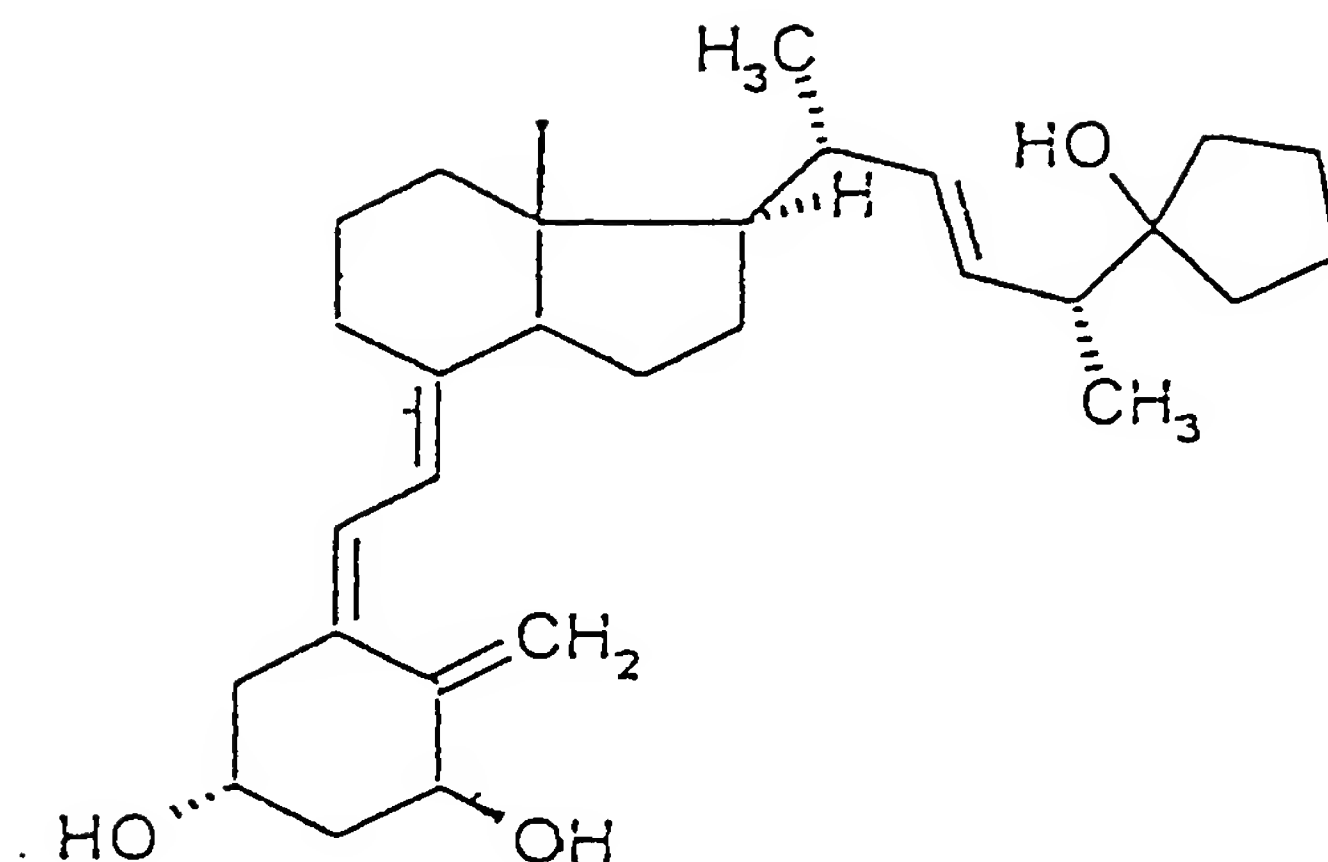
(QIX)



(QX)

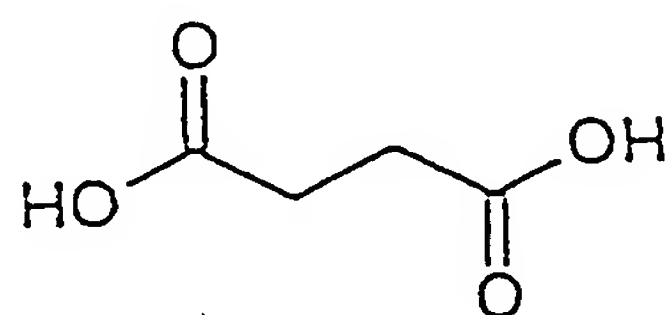


(QXII)



(QXI)

- succinic acid (RI)



(RI)

The precursor compounds of B or B₁ of the above mentioned groups P, Q and R are prepared according to the known methods in the prior art and described for example in "The Merck Index", 12^a Ed. (1996), herein incorporated by reference.

The vitamin D₃ derivative with retinoic acid (QVIII) is prepared as described in JP 93039261 (ref. C.A. 119 117617); the formula (QIX) compound according to EP 562497; 24,28-

methylene-1 α -hydroxyvitamin D2 (QX) according to EP 578494; the derivative compound of dehydroxyvitamin D2 (QXI) according to EP 549,318.

The precursors of B or B₁ which meet test 4, are preferred.

The tests carried out to identify the precursors of B or B₁ are in detail the following:

Test 4 is a colorimetric test which affords to establish whether the precursors of B or B₁ inhibit the production of radicals from DPPH (2,2-diphenyl-1-picryl-hydrazyl) (M.S. Nenseter et Al., Atheroscler. Thromb. 15, 1338-1344, 1995). 100 μ M solutions in methanol of the tested substances are prepared, and an aliquot of each of said solutions is added to a DPPH solution in methanol 0.1 M. After having stored the solutions at room temperature away from light for 30 minutes, their absorbances are read at the wave length of 517 nm, together with that of the corresponding DPPH solution at the same concentration. The absorbance decrease with respect to that of the solution of DPPH at the same concentration of the test solutions is determined. The effectiveness of the tested compound in inhibiting formation of radicals by DPPH is expressed by the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the test compound together with DPPH and of

the solution containing only DPPH; the compounds precursor of B or B₁ meet test 4 when the inhibition percentage of radical production from DPPH, expressed as a percentage according to the above equation, is higher than or equal to 50% at the indicated concentration (10^{-4} M).

If the precursors of B or B₁ do not meet test 4, test 5 is carried out.

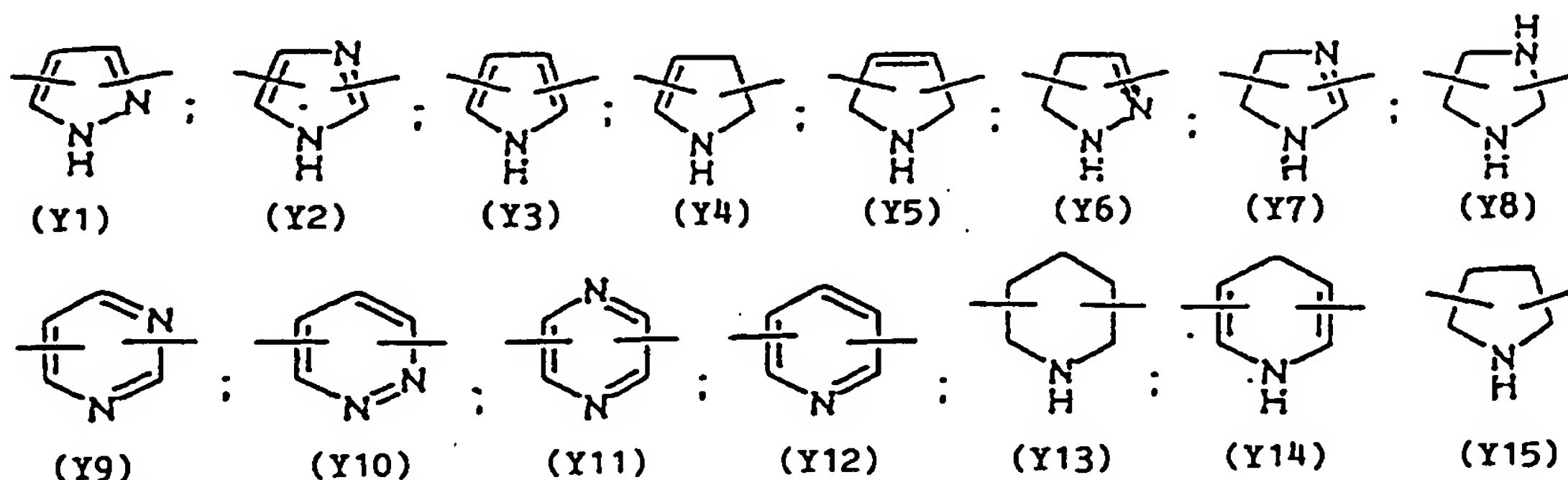
Test 5 is a colorimetric test wherein 0.1 ml aliquots of 10^{-4} M methanolic solutions of the tested products are added to test tubes containing a solution formed by 0.2 ml of 2 mM desoxyribose, 0.4 ml of phosphate buffer pH 7.4 100 mM and 0.1 ml of 1 mM $\text{Fe}^{2+}(\text{NH}_4)_2(\text{SO}_4)_2$ in 2mM HCl. The test tubes are then maintained at 37°C for one hour. Then in each test tube 0.5 ml of a 2.8% solution in trichloroacetic acid water and 0.5 ml of an aqueous 0.1 M solution of thiobarbituric acid are added, in the order. A reference blank is formed by adding to a test tube containing only the above described aqueous solution of reactants 0.1 ml of methanol. The test tubes are closed and heated in an oil bath at 100°C for 15 minutes. A pink coloration is developed the intensity of which is proportional to the quantity of desoxyribose undergone to radical oxidative degradation. The solutions are cooled at room temperature and their absorbances are read at 532 nm against the blank. The inhibition induced by the precursor of B or B₁ or C = $-T_c - Y - H$ in comparison with the radical production by Fe^{II} is determined

by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound + the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage of radical production as above defined from the precursor of B or B₁ or C = -T_c-Y-H is higher than or equal to 50%.

Y³ in formula (III) is preferably selected from the following:



The most preferred of Y³ is Y12 (pyridyl) substituted in positions 2 and 6. The bonds can find also in asymmetric position, for example Y12 (pyridyl) can be substituted also in position 2 and 3; Y1 (pyrazol) may be 3,5-disubstituted.

The compounds according to the present invention of formula (I) and (II) can be transformed into the corresponding salts. For example one way to form salts is the following: when in the molecule one nitrogen atom sufficiently basic to be salified, in organic solvent such as for example acetonitrile,

tetrahydrofuran, is present, it is reacted with an equimolecular amount of the corresponding organic or inorganic acid.

Preferably in the formula of the invention compounds Y or Y' of formula (III) is present.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acids.

Examples of inorganic acids are: nitric, hydrochloric, sulphoric, phosphoric acids.

In the steroid precursors preferably $R'' = -CO-CH_2OH$, $-CH(CH_3)-CH_2-CH_2-COOH$.

Among the steroid precursors those having the hydroxyl function in position 3 or in position 11, or having in R'' an hydroxyl or carboxylic function in terminal position, are preferred.

The steroid precursors of A which can be mentioned and which are preferred, are those listed hereinunder, obtainable according to the processes known in the art.

As precursors and respective processes, those for example described in The Merck Index, ed. 12 of 1996, herein incorporated by reference, can be mentioned. The precursors (according to the Merck nomenclature) are the following, wherein H_2 , H, R, R', R'' have the meaning mentioned in the compounds listed herein: Budesonide, Hydrocortisone, Alclomethasone, Algestone, Beclomethasone, Betamethasone, Chloro-

prednisone, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Cortisone, Corticosterone, Deflazacort, Desonide, Desoximethasone, Dexamethasone, Diflorasone Diflucortolone, Difluprednate, Fluazacort, Flucloronide, Flumethasone, Flunisolide, Fluocinolone Acetonide, Fluocinonide, Fluocortyn Butyl, Fluocortolone, Fluorometholone, Fluperolone Acetate, Fluprednidene Acetate, Fluprednisolone, Flurandrenolide, Formocortal, Halcinonide, Halobetasol Propionate, Halomethasone, Halopredone Acetate, Hydrocortamate, Loteprednol Etabonate, Medrysone, Meprednisone, Methylprednisolone, Momethasone Furoate, Paramethasone, Prednicarbate, Prednisolone, Prednisolone 25-Diethylaminoacetate, Prednisolone Sodium Phosphate, Prednisone, Prednival, Prednylidene, Rimexolone, Triamcinolone, Triamcinolone Acetonide, 21-Acetoxypregnenolone, Cortivazol, Amcinonide, Fluticasone Propionate, Mazipredone, Tixocortol, Triamcinolone Hexacetonide, Ursodesoxycholic acid, Chenodeoxycholic acid, Mitatrienediol, Moxestrol, Ethynylestradiol, Estradiol, Mestranol.

Unexpectedly the invention products of the formulas (I) and (II), in conditions of oxidative stress, have an improved therapeutic index compared with the precursor steroids. For illustrative purposes the above mentioned tests are referred to the following compounds (see the tables attached to the description):

Test 4 (test for the precursor of B and B₁, ref. Table III)

N-acetylcysteine inhibits of 100% radical production from DPPH, therefore it meets test 4 and it can be used as precursor of B or B₁.

4-thiazolidincarboxylic acid does not inhibit radical production from DPPH, therefore it does not meet test 4: it can be used as precursor of B or B₁ if it meets test 5.

Test 5 (test for the precursor of B and B₁ or of C= -T_c-Y-H, ref. Table IV)

4-thiazolidincarboxylic acid meets test 5 since the inhibition is of 100%. Therefore the compound can be used as precursor of B or B₁ in formula (I).

The compounds of the invention can be used in the same therapeutic indications of the precursor drug with the above mentioned advantages.

The compounds of formula (I) or (II) are prepared by synthesis methods mentioned hereinunder.

The choice of the reactions for each method depends on the reactive group present in the steroid molecule, in the precursor compound of B or B₁, which can be, as above mentioned, bivalent or monovalent, and in the precursor compound of C.

The reactions are carried out with well known methods in the prior art, which allow to obtain bonds among the steroid, the precursor compound of B or B₁ and the precursor compound of

C as above defined.

When the reactive function of the steroid (for example -COOH, -OH) is involved in a covalent bond, for example of ester, amide, ether type, said function can be restored with the well known methods in the prior art.

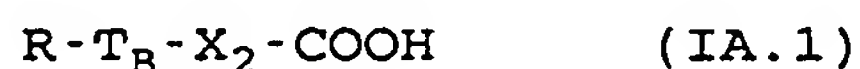
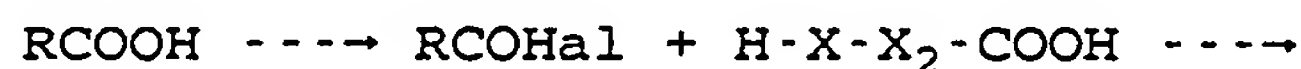
Some synthesis schemes for obtaining the compounds of the invention are reported hereinafter:

A) Synthesis of the compounds of formula (I).

1. Synthesis of the compound obtained by reaction between the steroid and the compound precursor of B.

1a. When the steroid contains a carboxylic function (general formula: R-COOH) and the functional group of the precursor compound of B which binds itself to the carboxylic function has the formula XZ, X being as above defined and Z = H, the effected reactions depend on the nature of the second reactive group present in the precursor compound of B.

1a.1 When the second reactive group present in the precursor compound of B is a carboxylic group, the synthesis general scheme expects the initial formation of the acyl halide of the R-COHal steroid (Hal = Cl, Br) and the subsequent reaction with the HX group of the precursor compound of B:



X_2 , T_B being as above defined.

When in the two reaction compounds other functional groups COOH and/or HX are present, they must be protected before the reaction according to the methods known in the prior art; for example as described in the publication by Th. W. Greene: "Protective groups in organic synthesis", Harward University Press, 1980.

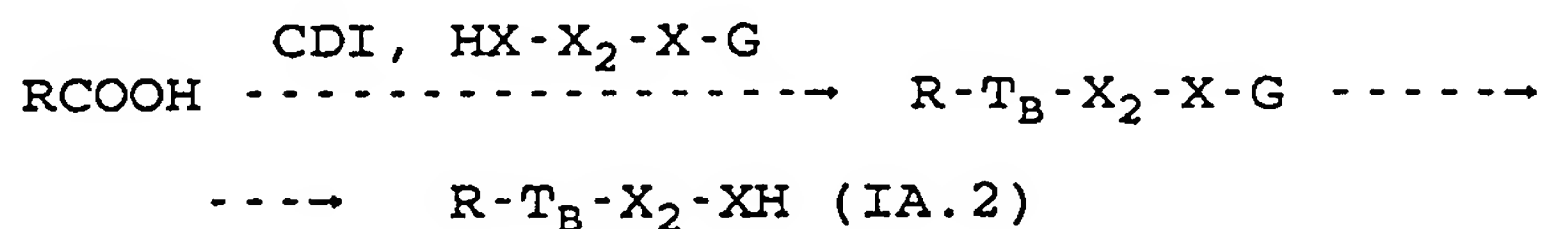
The RCOHal acylhalide is prepared according to the known methods in the prior art, for example by thionyl or oxalyl chloride, P^{III} or P^V halides in inert solvents under the reaction conditions, such as for example toluene, chloroform, DMF, etc.

Specifically, when the HX group of the precursor compound of B is NH_2 , or OH or SH, the steroid of formula R-COOH is first converted into the corresponding acyl halide RCOHal, as above mentioned, and then reacted with the HX group of the precursor compound of B in the presence of an organic base, such as triethylamine, pyridine, etc. using an inert solvent in the reaction conditions such as toluene, tetrahydrofuran, etc. at a temperature in the range 0°C-25°C.

Alternatively to the previous synthesis, the steroid of formula R-COOH can be treated with an agent activating the carboxyl group selected from N,N'-carbonyldiimidazol (CDI), N-hydroxybenzotriazol and dicyclohexylcarbodiimide

in solvent such as for example DMF, THF, chloroform etc.
at a temperature in the range -5°C - 50°C and the obtained
compound reacted in situ with the reactive function of
the precursor compound of B for obtaining the compound of
formula (IA.1).

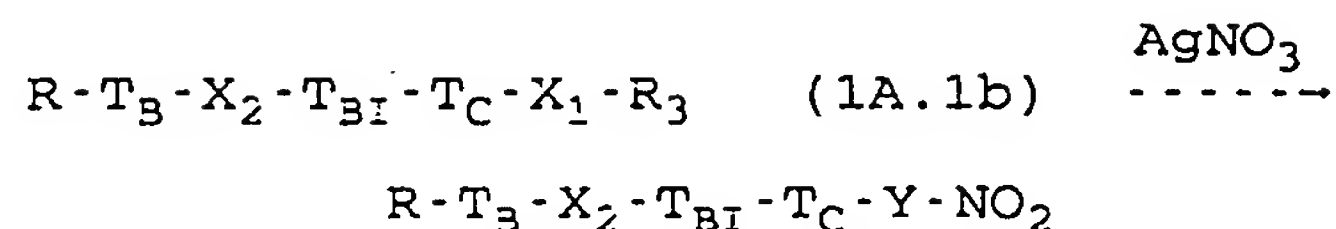
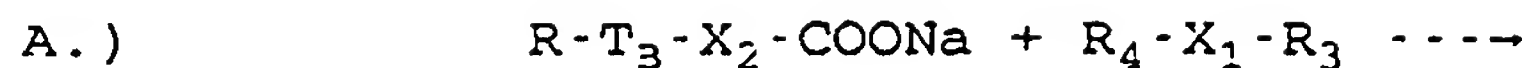
1a.2 When the precursor compound of B contains two functional
groups XZ, equal to or different from each other, X being
as above defined and Z = H, the steroid having formula R-
COOH is first treated with an agent activating the
carboxyl group, as above described in 1a.1, and then with
the precursor compound of B, after having protected one of
the two reactive HX groups, for example with acetyl or
tert-butyloxycarbonyl, restoring the initial function at
the synthesis end. The scheme is the following:



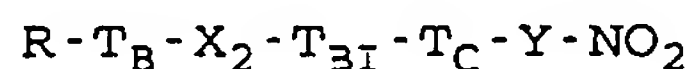
wherein X, T_B, X₂ are as above defined and G is a
protective group of the HX function.

2. Nitroxyderivative synthesis.

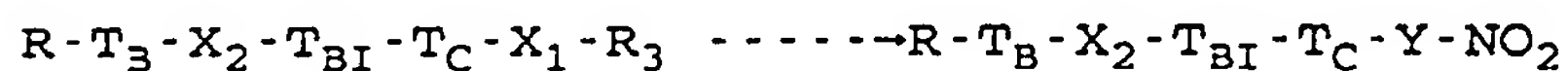
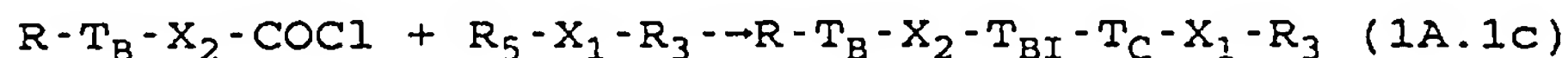
2a.1 When the compound obtained at the end of the previous step
1a. has formula (IA.1), the acid can be converted into the
corresponding sodic salt and one can then follow the known
prior art methods for preparing the final compound, for
example according to one of the following synthesis
schemes:



wherein T_B , X_2 , T_{BI} , T_C are as above defined, R_4 is selected from Cl, Br, Y is as above defined, X_1 is the Y radical free from the oxygen atom, R_3 is Cl, Br, Iodine, OH. If $R_3 = OH$ the compound of formula (1A.1b) is subjected to halogenation, for example with PBr_3 , PCl_5 , $SOCl_2$, $PPh_3 + I_2$, and then reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran. If R_3 is Cl, Br, Iodine, the compound of formula (1A.1b) is directly reacted with $AgNO_3$ as above mentioned.



C.)

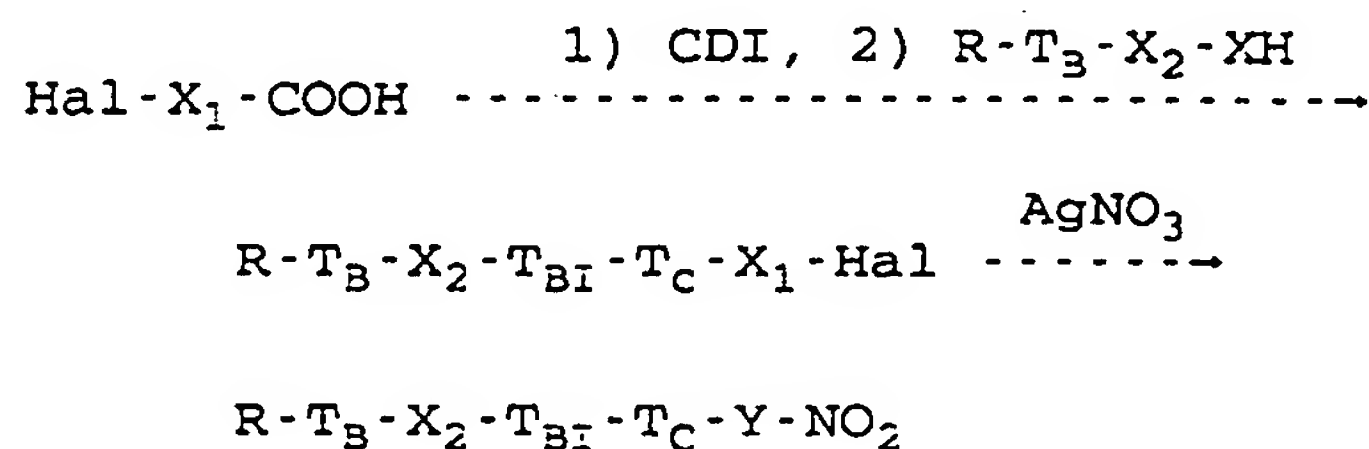


wherein $R_5 = OH$ or NHR_{1C} , R_{1C} , R_3 and the other symbols being as above defined.

When X_1 is a linear C_4 alkyl, the corresponding acid $R-T_B-X_2-COOH$ is reacted with triphenylphosphine in the presence of an halogenating agent such as CBr_4 or N-bromosuccinimide in tetrahydrofuran obtaining the compound

(1A.1c) wherein $R_3 = \text{Br}$.

2a.2 When the compound obtained at the end of the previous step 1a. has formula (IA.2), the corresponding nitroxyderivative is obtained by treating an halogen-carboxylic acid of formula $\text{Hal-X}_1\text{-COOH}$, X_1 being as above defined, first with an agent activating the carboxyl group as described in 1A.1, and then with the compound of formula (IA.2), obtaining an halogen derivative, which is isolated and then dissolved in organic solvent, (ref. paragraph 2a.1), and treated with silver nitrate. The global reaction scheme is the following:



wherein T_B , X_2 , T_{BI} , T_C , Y are as above defined.

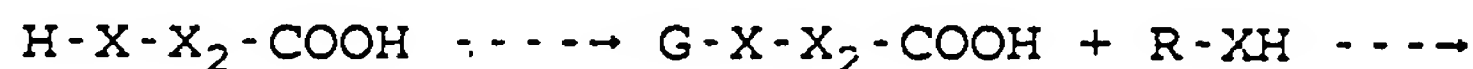
Alternatively, the halide $\text{Hal-X}_1\text{-COCl}$ can be used, wherein Hal is preferably bromine, which is let react with the compound of formula (IA.2).

1b. When the reactive function of the steroid is $-\text{OH}$ (general formula: R-OH), the two functional groups present on the precursor compound of B can be the following:

1b.1 A carboxylic group, which reacts with the steroid OH function, and a HX group, the latter reactive group of the precursor compound of B being equal to or different from

the steroid functional group. The formula of the precursor compound of B is of the $H-X-X_2-COOH$ type, wherein X and X_2 are as above defined.

The H-X- function of the precursor compound of B is protected according to the known prior art methods and the carboxyl is reacted, as above mentioned, according to the following scheme:



At the end of the reaction the HX function of the precursor compound of B is restored.

1b.2 When the precursor compound of B contains two carboxylic groups, it is treated with an equimolar amount of an agent activating the carboxyl group under the conditions previously described in 1a.1, and then reacted with the reactive OH function of the steroid molecule. Possible other reactive functions of HX type present in the two compounds must be carefully protected as previously mentioned. Lastly a compound of formula $R-T_B-X_2-COOH$ (1B.2) is obtained.

2b. Nitroxyderivative synthesis.

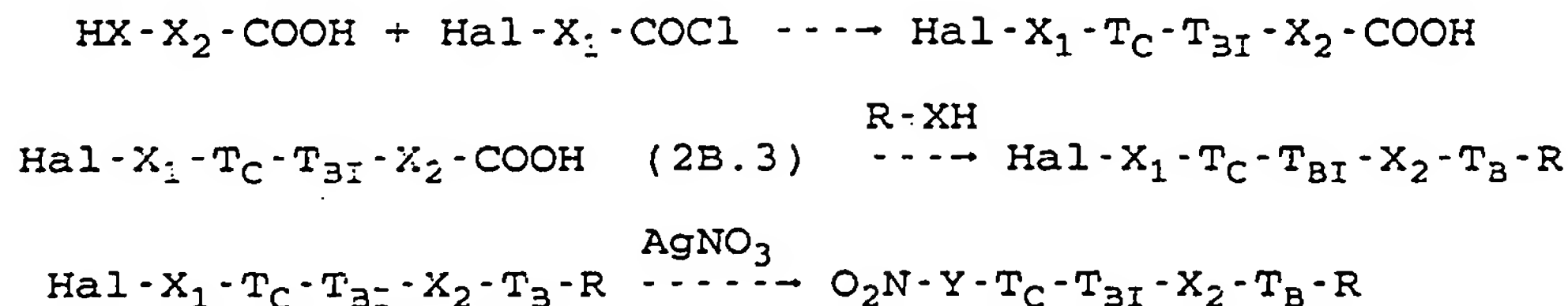
2b.1 To obtain the final nitroxyderivative starting from the compound of formula $R-T_B-X_2-X-H$ (1B.1), obtained at the end of the synthesis described in 1b.1, the (1B.1) compound is reacted with an halogenacid of formula $Hal-X_1-$

COOH which has been treated as previously described in paragraph 1a.1, or with the corresponding halogenacid chloride, the resulting compound is dissolved in organic solvent, for example acetonitrile or tetrahydrofuran and reacted with silver nitrate.

2b.2 To obtain the final nitroxyderivative starting from the compound of formula $R-T_3-X_2-COOH$ (1B.2), obtained at the end of the synthesis described in 1b.2, the acid is transformed into the corresponding sodic salt, it is reacted with a $R_4-X_1-R_3$ compound, previously defined in the reaction A. scheme of paragraph 2a.1, obtaining according to the same process therein mentioned the final nitroxyderivative. Alternatively, when X_1 is a linear C_4 alkyl, the acid (1B.2) is reacted with triphenyl-phosphine in the presence of an halogenating agent such as CBr_4 or N-bromosuccinimide in tetrahydrofuran and the resulting compound dissolved in organic solvent for example acetonitrile, tetrahydrofuran, is reacted with silver nitrate.

2b.3 Alternatively to the synthesis process according to 1b.1 and 2b.1, it is possible to react in a first step the HX-function of the precursor compound of B $HX-X_2-COOH$ with the acyl chloride of an halogenacid of formula $Hal-X_1-CO-Cl$, wherein Hal is preferably Br, and subsequently the carboxylic function of the so obtained compound, with the

steroid of formula R-OH. In the third and last step the Hal group is substituted with -ONO₂ according to the process described in 2b.1. The reaction scheme is the following:



wherein T_C, T_{3I}, T₃, X₂, X₁, Y are as above defined.

In the previous scheme the nitration can alternatively be carried out on the acid compound of formula (2B.3).

In the above mentioned processes the steroid reaction with the precursor of B for the compounds of formula (I) is not carried out when b₀ = 0, and in the reaction with the precursor compound of C the steroid with its reactive function is directly used.

B) Synthesis of compounds of formula (II).

1a. When the steroid reactive function is a carboxylic group and the precursor compound of B₁ contains only one functional reactive group of formula XH, X being as above defined, the steroid is initially converted into the corresponding acyl-halide (RCOCl), or treated with an agent activating the carboxyl group as described in 1a.1, and then reacted with the HX function of an halogen-acid compound, said function being equal to or different from that present on the precursor compound of B₁, said

halogen-acid having the formula:

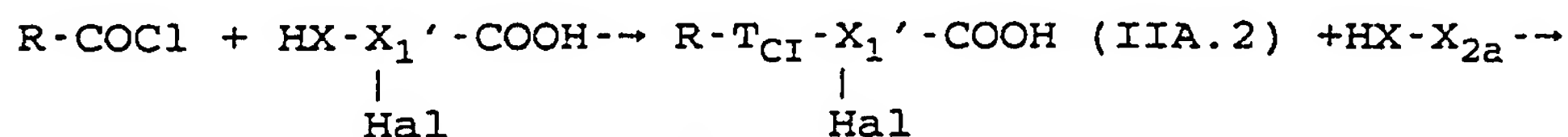


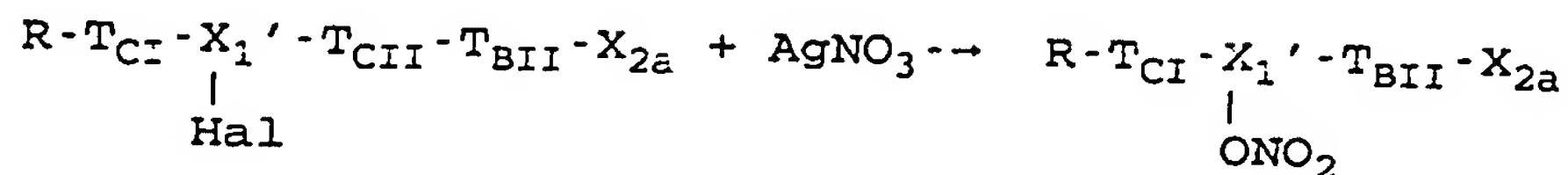
wherein $X_1\text{'}$ is $Y\text{'}$ as above defined without the oxygen atom through which the $-\text{NO}_2$ group is linked, X and Hal are as above defined.

The compound (IIA.1) can be obtained with the known method of the prior art.

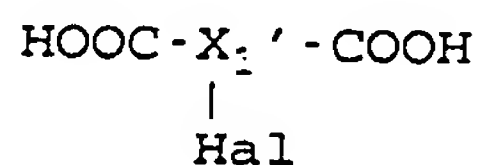
For example when $X = \text{NH}$, it can be obtained from the corresponding hydroxy-aminoacid, by protecting the aminic group by the corresponding tert-butyl-oxycarbonyl derivative and transforming the hydroxyl function into halogen group as described for the compound halogenation (1A.1b) in 2a.1.

The free carboxylic function of the compound resulting from the reaction with the steroid molecule is reacted with the function present in the molecule of the precursor of B_1 , as previously illustrated in 1a.1 for the reaction between the steroid of formula $R\text{-COOH}$ and the precursor compound of B . In the final step the halogen atom (Hal) present on the radical X_1 is substituted with an ONO_2 group by adding AgNO_3 to an organic solution of the compound. The reaction scheme is the following, exemplified starting from the RCOCl halide:

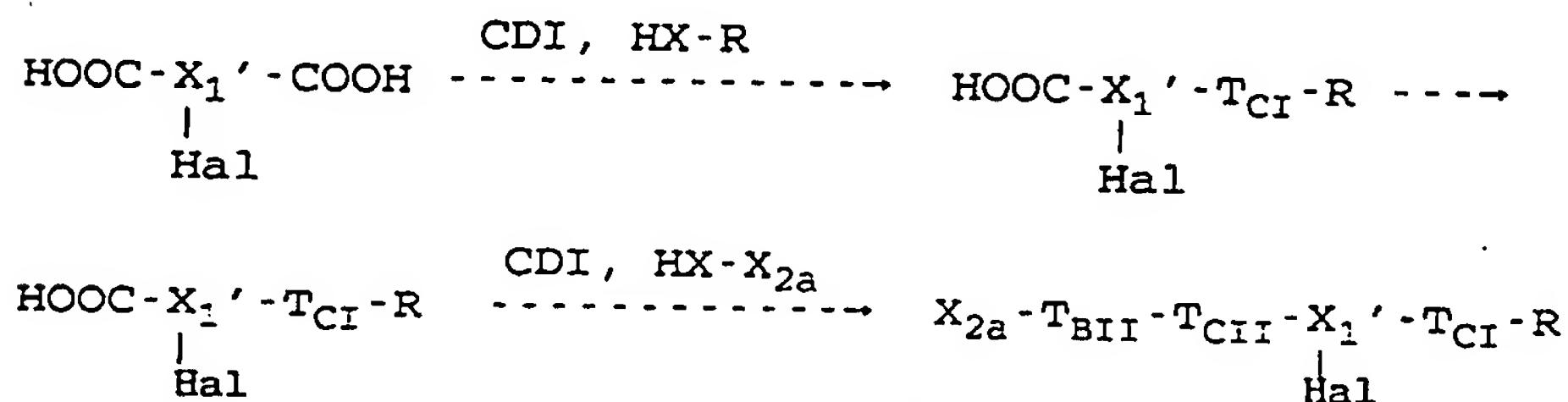




- 1b. When the steroid reactive function is a OH group and the precursor compound of B₁ contains a reactive group of general formula XH, HX wherein X is as above defined, being equal to or different from OH, the synthesis is carried out starting from an halogendiacid compound of formula



X₁' being as above defined, said compound being prepared from the corresponding hydroxy-diacid as described for the halogenation of the compound (1A.1b) in 2a.1. The halogendiacid compound is treated with an equimolar amount of an agent activating the carboxyl group, under the conditions previously described in 1a.1., and then it is reacted with the reactive function of the steroid molecule. In the subsequent step the second carboxylic function is treated with an activating agent, as previously made for the first, and reacted with the precursor compound of B₁ according to the following scheme:



The halogen atom is then substituted with the ONO_2 group as above mentioned.

3. Synthesis of the nitroso ($s=1$) derivatives of formula (I).

3a.1 The compound of formula (1A.1b) wherein $\text{R}_3 = \text{OH}$ is reacted with sodium nitrite in a solvent formed of a mixture of water with tetrahydrofuran in the presence of hydrochloric acid. The reaction is widely illustrated in the prior art. The general scheme is the following:



3a.2 If the compound obtained at the end of step A has formula (IA.2) the corresponding nitroso derivative is obtained by treating an hydroxyacid of formula $\text{HO-X}_1-\text{COOH}$, X_1 being as above defined, first with an agent activating the carboxyl group, as described in 1a.1, then with 1A.2 and the resulting product with sodium nitrite as described in 3a.1.

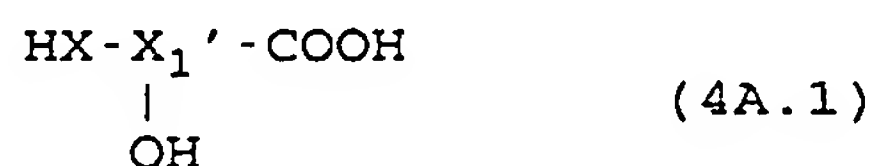
3b.1 To obtain the nitroso derivative starting from the compound of formula $\text{R-T}_\text{B}-\text{X}_2-\text{XH}$ (1B.1) obtained at the end of the synthesis described in 1b.1, the compound (1B.1) is reacted with an hydroxyacid as described in 3a.2.

3b.2 To obtain the nitroso derivative from the compound of formula $\text{R-T}_\text{B}-\text{X}_2-\text{COOH}$ (1B.2) obtained at the end of the synthesis described in 1b.2, the acid is transformed into the sodic salt and reacted with a compound $\text{Hal-X}_1-\text{OH}$, as

previously described, and the obtained alcohol is treated as described in 3a.1.

4) Synthesis of the nitroso derivatives of formula (II)

4a.1 When the steroid reactive function is a carboxylic group (general formula R-COOH) and the precursor compound of B₁ contains only one functional reactive group of formula XH, X being as above defined, R-COOH is initially converted into the corresponding acyl-halide or treated with an agent activating the carboxyl group as described in 1a.1, and then reacted with the HX function of an hydroxy-acid compound, said function being equal to or different from that present on the precursor compound of B₁, said hydroxy-acid having the formula:

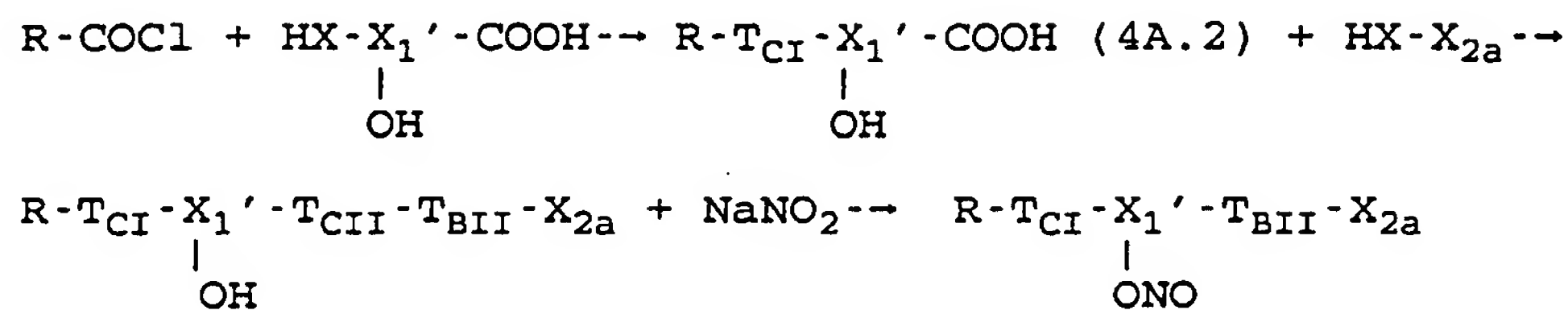


wherein X₁' is Y' as above defined without the oxygen atom through which the -NO group is linked, X is as above defined.

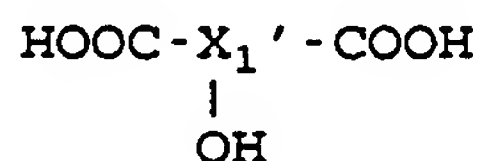
The free carboxylic function of the compound resulting from the reaction with the steroid molecule is reacted with the function present in the molecule of the precursor compound of B₁, as previously illustrated in 1a.1 for the reaction between the R-COOH acid and the precursor compound of B. In the final step the alcohol is transformed into the nitroso-derivative as described in

3a.1.

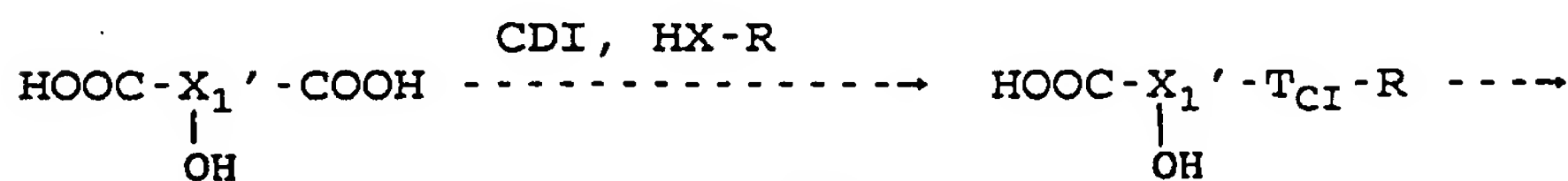
The reaction scheme is the following, exemplified starting from the RCOCl acid halide:

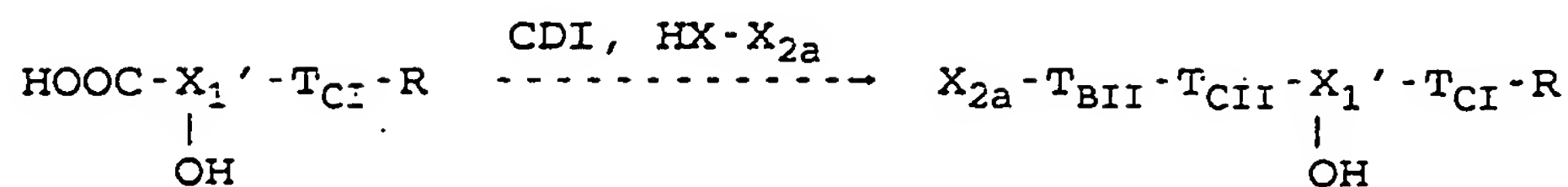


4b. When the reactive steroid function is a OH group and the precursor compound of B₁ contains a reactive group of general formula XH, HX in which X is as above defined being equal to or different from OH, the synthesis is carried out starting from an hydroxydiacid compound of formula



X_1' being as above defined, said hydroxydiacid compound is treated with an equimolar amount of an agent activating the carboxyl group, under the conditions previously described in 1a.1., and then it is reacted with the steroid reactive function. In the subsequent step the second carboxylic function is treated with an activating agent, as previously made for the first one, and reacted with the precursor compound of B_1 according to the following scheme:





The obtained compound is reacted as described in 3a.1.

The compounds object of the present invention are formulated in the corresponding pharmaceutical compositions for parenteral, oral and topic use according to the well known methods in the art, together with the usual excipients; see for example the volume "Remington's Pharmaceutical Sciences 15a Ed."

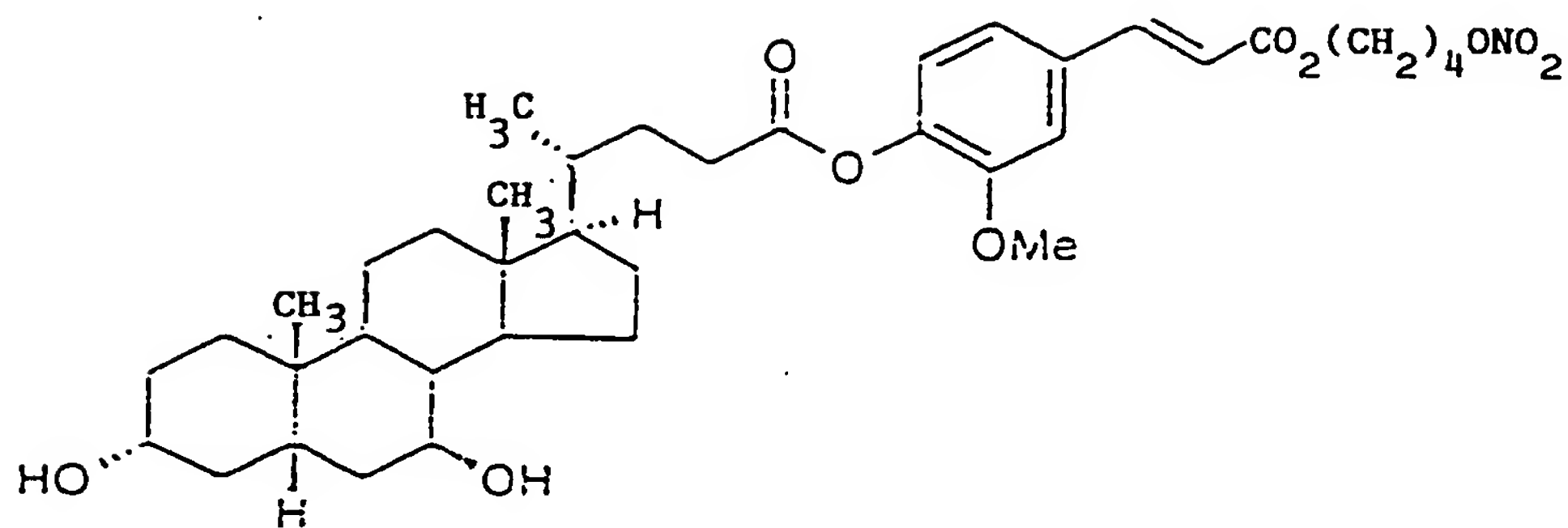
The amount on molar basis of the active principle in these formulations is the same, or lower, in comparison with that used of the corresponding precursor drug.

The daily administrable doses are those of precursor drugs, or in the case lower. The daily doses can be found in the publications of the field, such as for example in "Physician's Desk reference".

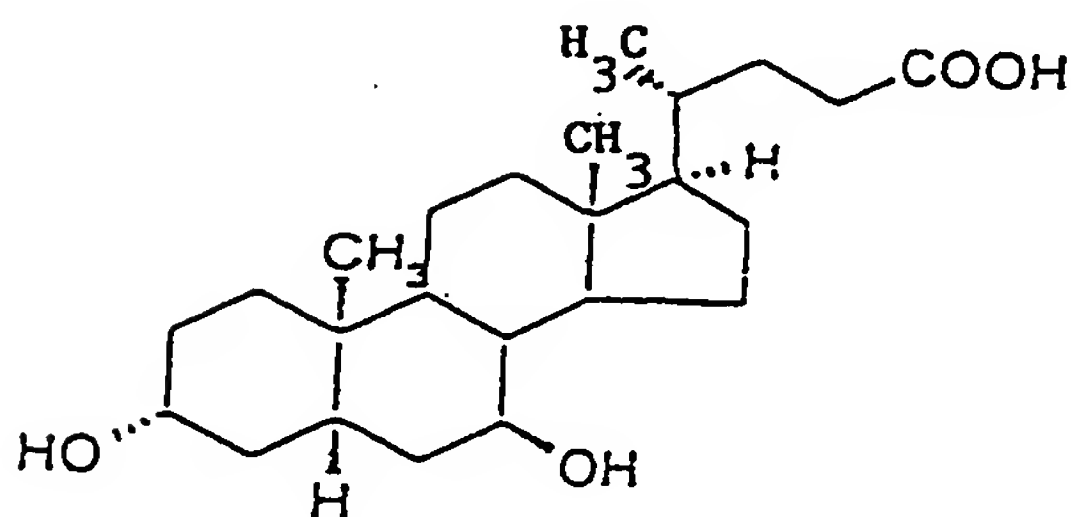
The following examples have the purpose to illustrate the invention and are not to be considered as limitative of the same.

EXAMPLE 1

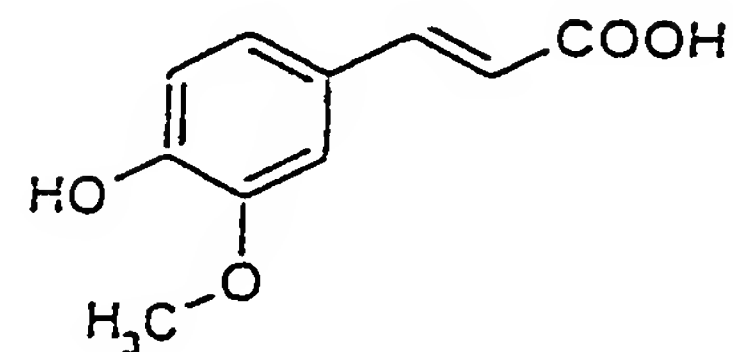
Preparation of 3-[4-[(3 α ,5 β ,7 β)-3,7-dihydroxycolan-24-oiloxy]-3-methoxyphenyl]-2-propenoic acid 4-nitroxybutyl ester



wherein the precursor steroid is ursodesoxycholic acid of formula (XL), the precursor of B is ferulic acid of formula (DII):



(XL)



(DII)

a) synthesis of the 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-bromobutyl ester

To a solution of 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid (10 g, 51.5 mmol) in THF (400 ml) triphenylphosphine (2.7 g, 10.3 mmol) and carbon tetrabromide (34.16 g, 10.3 mmol) are added and the solution is left at room temperature,

under magnetic stirring, for 48 hours. The solid is filtered and then evaporated at reduced pressure. The obtained crude product is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 9 g of 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-bromobutyl ester are obtained. M.p. = 86-89°C.

b) Synthesis of the 3-[4-[(3 α ,5 β ,7 β)-3,7-dihydroxycolan-24-oiloxy]-3-methoxyphenyl]-2-propenoic acid 4-bromobutyl ester

To a solution of (3 α ,5 β ,7 β)-3,7-dehydroxycolan-24-oic acid (2.9 g, 7.38 mmol) dissolved in chloroform (25 ml) and dimethylacetamide (25 ml), 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-bromobutyl ester (2.73 g, 8.28 mmol) is added under stirring. To the solution cooled at 0°C, kept under stirring, N,N'-dicyclohexylcarbodiimide (2 g, 9.7 mmol) and 4-dimethylamino pyridine (100 mg, 0.81 mmol) are added. After 1 hour the mixture is heated to room temperature, after 24 hours the precipitate is filtered, the solvent is evaporated at reduced pressure. The residue is treated with ethyl acetate (150 ml) and washed with water (3X 100 ml). After the organic phase is anhydriified with sodium sulphate the solvent is evaporated. The obtained crude product is purified by chromatography on silica gel column eluting with n-hexane/ethyl acetate 1/9. 2.5 g of 3-[4-[(3 α ,5 β ,7 β)-3,7-dihydroxycolan-24-oiloxy]-3-methoxyphenyl]-2-propenoic acid 4-bromobutyl ester are obtained.

c) Synthesis of the 3-[4-[(3 α ,5 β ,7 β)-3,7-dihydroxycolan-24-oiloxy]-3-methoxyphenyl]-2-propenoic acid 4-nitroxybutyl ester

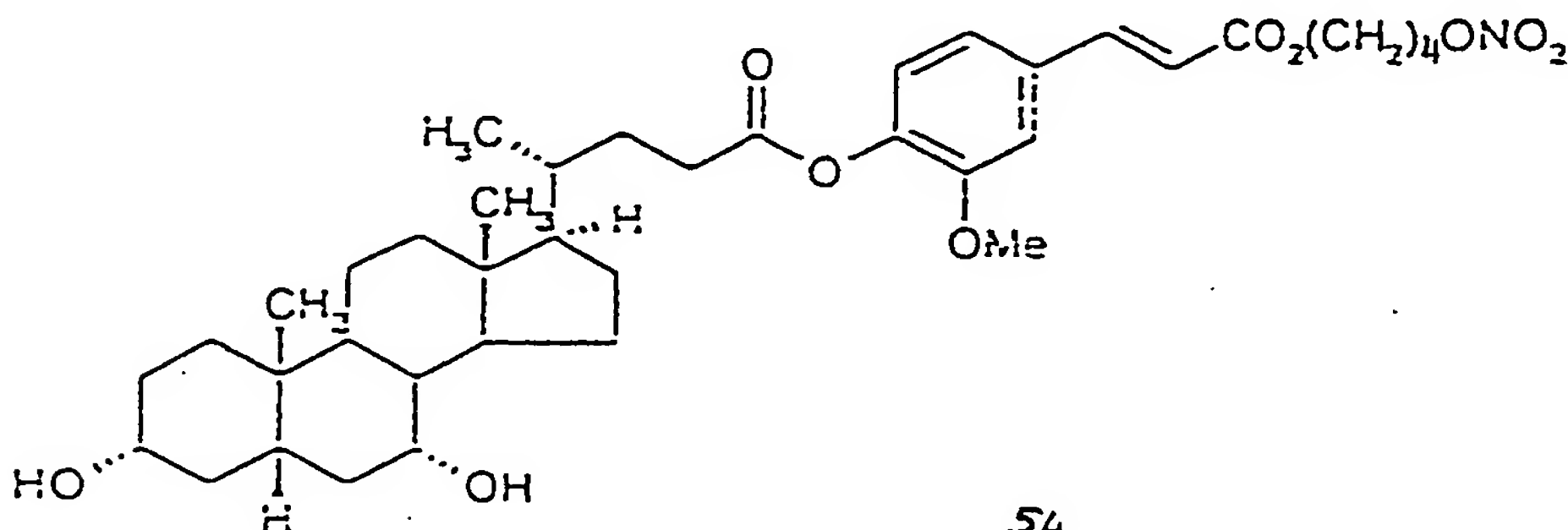
To a solution of 3-[4-[(3 α ,5 β ,7 β)-3,7-dehydroxycolan-24-oiloxy]-3-methoxyphenyl]-2-propenoic acid 4-bromobutyl ester (2.3 g, 3.27 mmoles) in acetonitrile (20 ml) and tetrahydrofuran (5 ml) silver nitrate (0.84 g, 4.94 mmoles) is added under stirring and the mixture is heated to 80°C under magnetic stirring for 6 hours. When the reaction is over the precipitate is filtered and the solvent is evaporated. The obtained crude product is purified by chromatography on silica gel column eluting with methylene chloride/ethyl acetate 3/7. 1.5 g of 3-[4-[(3 α ,5 β ,7 β)-3,7-dehydroxycolan-24-oiloxy]-3-methoxyphenyl]-2-propenoic acid 4-nitroxybutyl ester are obtained. Total yield 32%.

Elementary analysis

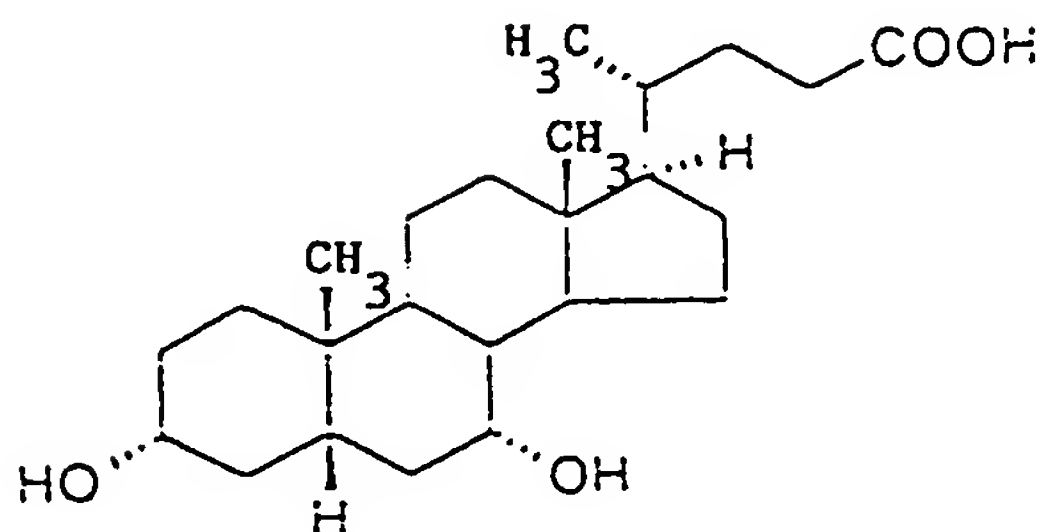
Calculated	C	66.55%	H	8.08%	N	2.04%
Found	C	66.59%	H	8.14%	N	1.99%

EXAMPLE 2

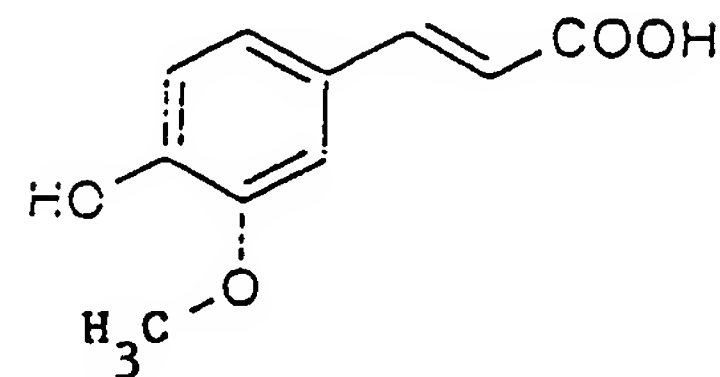
Preparation of 3-[4-[(3 α ,5 β ,7 α)-3,7-dihydroxycolan-24-oiloxy]-3-methoxyphenyl]-2-propenoic acid 4-nitroxybutyl ester



wherein the precursor steroid is chenodeoxycholic acid of formula (XLI) and the B precursor is ferulic acid of formula (DII)



(XLI)



(DII)

The compound is prepared following the procedure reported in Example 1. Total yield 28%.

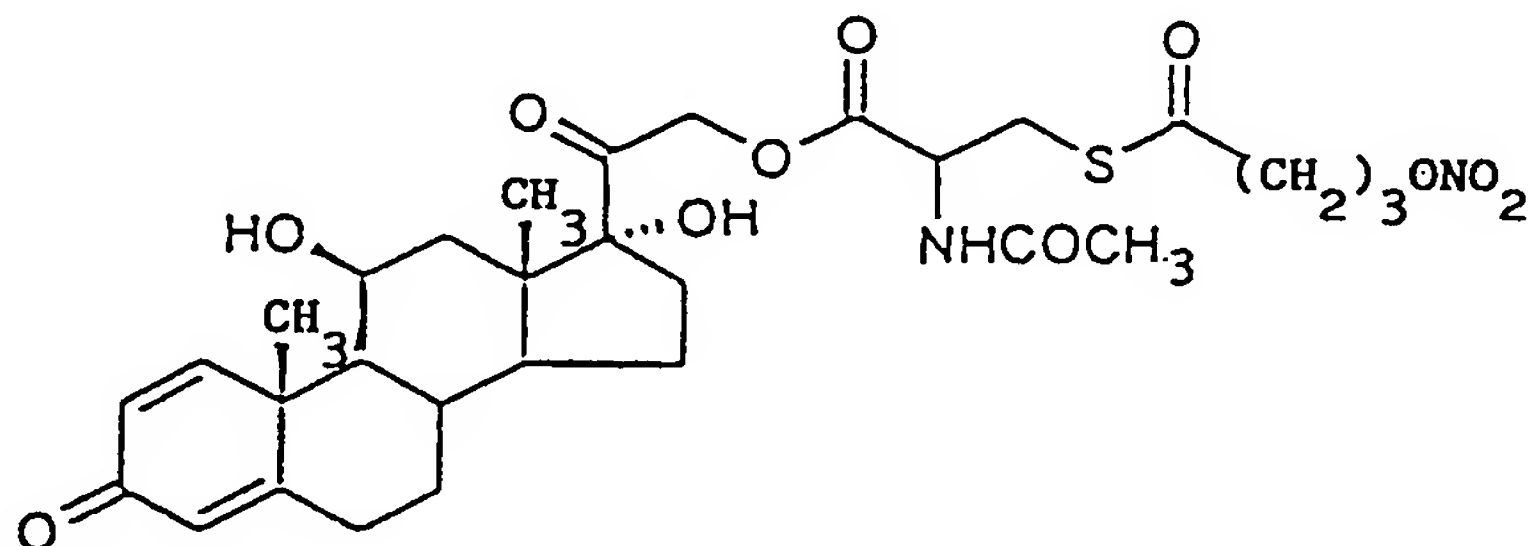
Elementary analysis

Calculated C 66.55% H 8.08% N 2.04%

Found C 66.64% H 8.13% N 1.94%

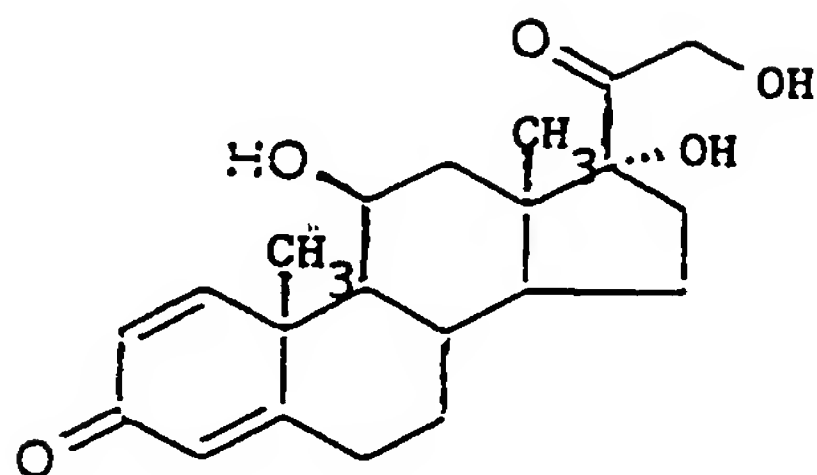
EXAMPLE 3

Preparation of (11 β)-11,17-dihydroxy-21[N-acetyl-S-(4-nitroxybutyroyl)cysteinyloxy]-pregn-1,4-diene-3,20-dione

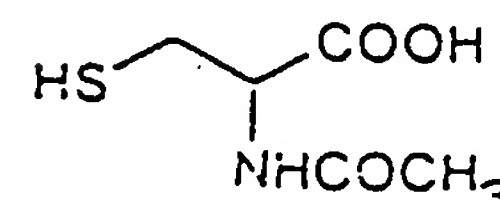


wherein the precursor steroid is prednisolone of formula (XLII)

and the precursor of B is N-acetyl cysteine of formula (CVIII)



(XLII)



(CVIII)

a) Synthesis of N-acetyl-S-(4-bromobutyroyl)cysteine

A solution of 4-bromobutyric acid (5.1 g, 30.6 mmol) and 1,1'-carbonyldiimidazole (5.61 g, 34.6 mmol) in chloroform (50 ml) is left at room temperature under stirring for 1 hour. To the reaction mixture N-acetyl cysteine (5 g, 30.6 mmol) dissolved in N,N-dimethylformamide (5 ml) and sodium ethylate (50 mg) is added under stirring. After 24 hours the solution is washed with HCl 1% and brine, the organic phase is anhydriified with sodium sulphate and evaporated at reduced pressure. The obtained crude product is purified by chromatography on silica gel column, eluting with ethyl acetate/chloroform 7/3. N-acetyl-S-(4-bromobutyroyl)cysteine is obtained.

b) Synthesis of (11 β)-11,17-Dihydroxy-21[N-acetyl-S-(4-bromobutyroyl)cysteinyloxy]-pregn-1,4-diene-3,20-dione

To a solution of N-acetyl-S-(4-bromobutyroyl)cysteine (2.7 g, 8.64 mmol) and (11 β)-11,17,21-trihydroxypregn-1,4-diene-3,20-dione (3.2 g, 8.86 mmol) in tetrahydrofuran (100

ml) cooled at 0°C and kept under stirring, N,N'-dicyclohexylcarbodiimide (1.9 g, 9.2 mmol) and 4-dimethylaminopyridine (100 mg, 0.8 mmol) are added. After 1 hour the mixture is heated to room temperature, after 24 hours the precipitate is filtered, the solvent is evaporated at reduced pressure. The residue is treated with ethyl acetate (150 ml) and washed with water (3X 100 ml). After having anhydri-fied the organic phase with sodium sulphate the solvent is evaporated. The obtained crude product is purified by chromatography on silica gel column eluting with chloroform/ethyl acetate 3/7. 0.94 g of (11 β)-11,17-dehydroxy-21[N-acetyl-S-(4-bromobutyroyl)cysteinyloxy]-pregn-1,4-diene-3,20-dione are obtained.

c) Synthesis of (11 β)-11,17-Dihydroxy-21[N-acetyl-S-(4-nitroxybutyroyl)cysteinyloxy]-pregn-1,4-diene-3,20-dione

To a solution of (11 β)-11,17-dehydroxy-21[N-acetyl-S-(4-bromobutyroyl)cysteinyloxy]-pregn-1,4-diene-3,20-dione (0.8 g, 1.28 mmol) in acetonitrile (10 ml) and tetrahydrofuran (5 ml) silver nitrate (0.4 g, 2.35 mmol) is added under stirring and the mixture is heated to 80°C under magnetic stirring for 20 hours. At the end of the reaction the precipitate is filtered and the solvent is evaporated. The obtained crude product is purified by chromatography on silica gel column eluting with methylene chloride/ethylacetate 3/7. (11 β)-11,17-dehydroxy-21[N-acetyl-S-(4-nitroxybutyroyl)cysteinyloxy]-pregn-1,4-diene-

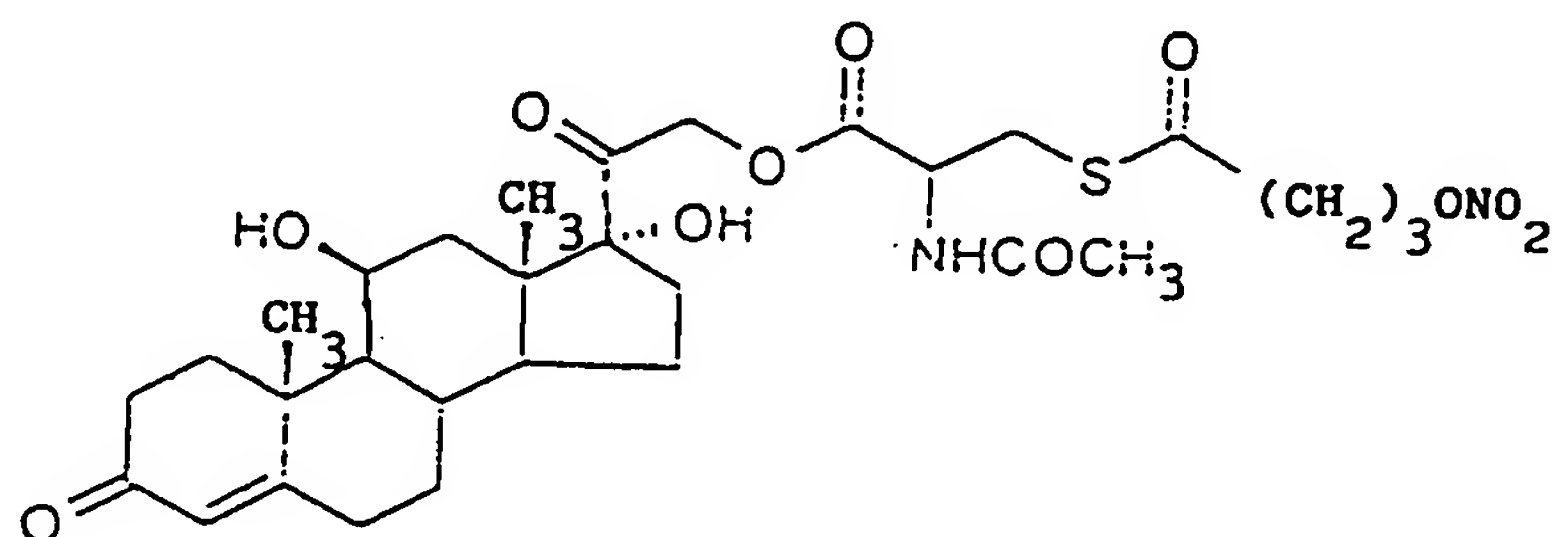
3,20-dione is obtained. Total yield 12%.

Elementary analysis

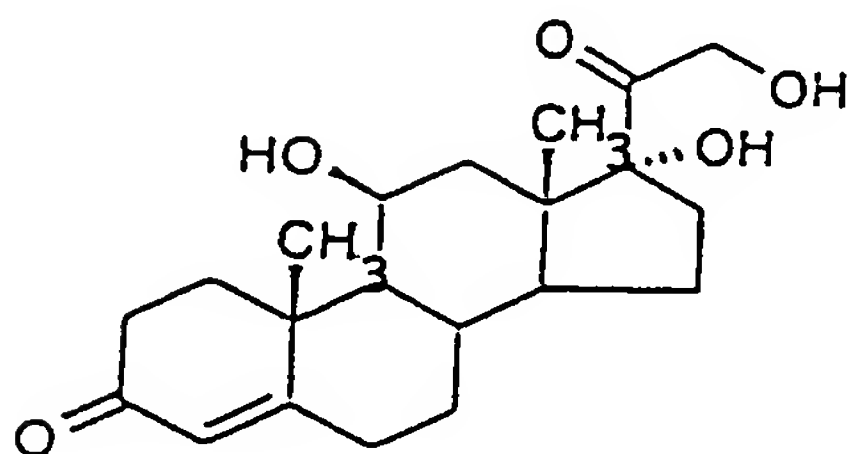
Calculated	C 56.59%	H 6.33%	N 4.40%	S 5.04%
Found	C 56.63%	H 6.38%	N 4.36%	S 5.01%

EXAMPLE 4

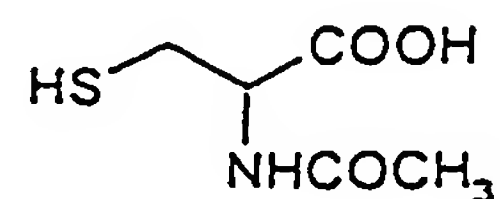
Preparation of (11 β)-11,17-Dihydroxy-21[N-acetyl-S-(4-nitroxybutyroyl)cysteinyl]oxy]-pregn-4-ene-3,20-dione



wherein the precursor steroid is hydrocortisone of formula (XLIII) and the precursor of B is N-acetyl cysteine of formula (CVIII)



(XLIII)



(CVIII)

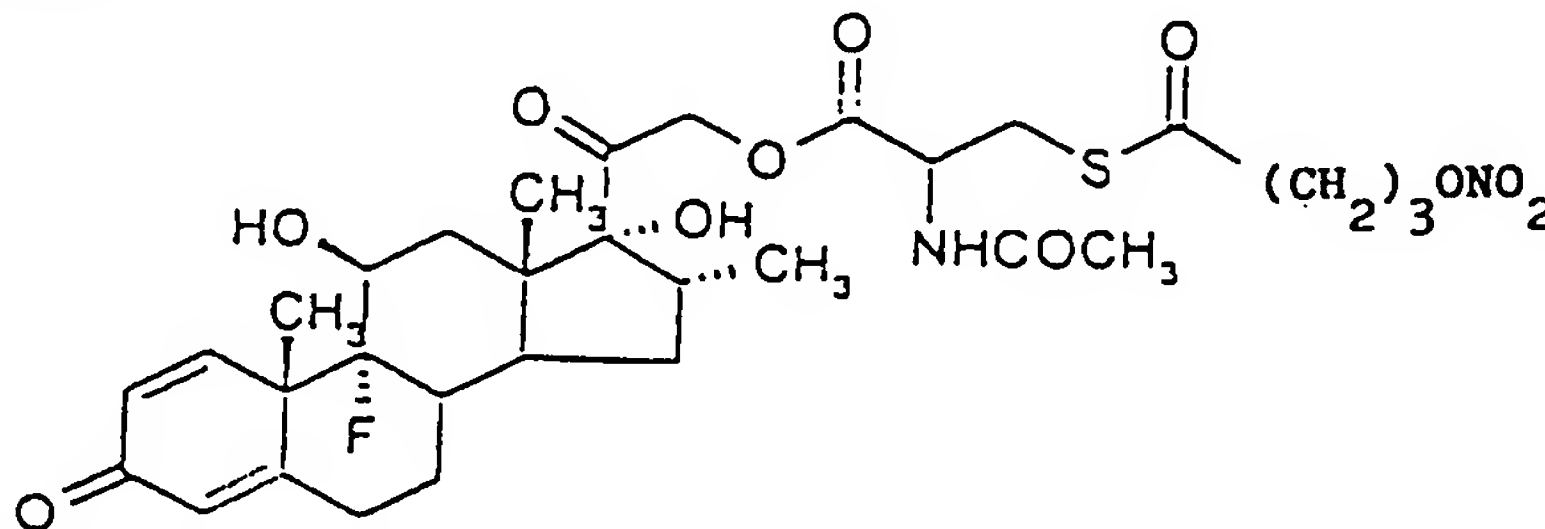
The compound is prepared according to the procedure reported in Example 3. Total yield 15%.

Elementary analysis

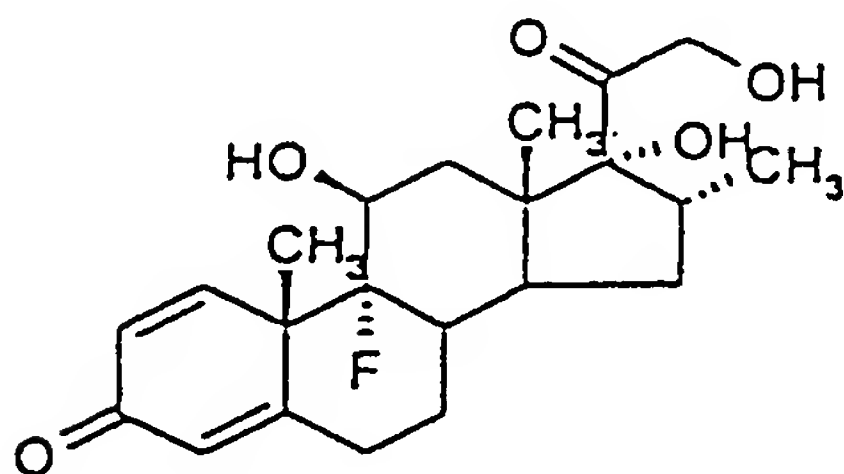
Calculated	C 56.37%	H 6.78%	N 4.39%	S 5.02%
Found	C 56.39%	H 6.81%	N 4.31%	S 4.93%

EXAMPLE 5

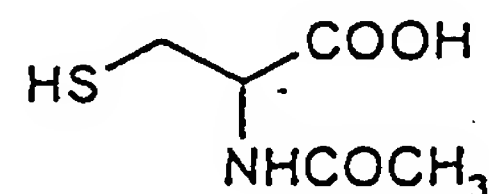
Preparation of (11 β ,16 α)-9-Fluoro-11,17-dihydroxy-21[N-acetyl-S-(4-nitroxybutyryl)cysteinyl]-16-methylpregn-1,4-diene-3,20-dione



wherein the precursor steroid is desamethasone of formula (XLIV) and the precursor of B is N-acetyl cysteine of formula (CVIII)



(XLIV)



(CVIII)

The compound is prepared according to the procedure reported in Example 3. Total yield 17%.

Elementary analysis

Calculated	C 55.68%	H 6.18%	N 4.19%	S 4.79%
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Found C 55.72% H 6.22% N 4.15% S 4.75%

PHARMACOLOGICAL TESTS

EXAMPLE

Acute Toxicity

Acute toxicity has been evaluated by administering to a group of 10 rats weighing 20 g a single dose of each of the tested compounds, by cannula, by os in an aqueous suspension of carboxymethylcellulose 2% w/v.

The animals are kept under observation for 14 days. In no animal of the group toxic symptoms appeared even after a 100 mg/Kg dose administration.

EXAMPLE F1

Experimental in vivo model with N^w-nitro-L-arginine-methyl ester (L-NAME): effect of the precursor steroids and of the corresponding compounds according to the present invention on the endothelial dysfunction induced by L-NAME.

The experimental model adopted is according to J. Clin. Investigation 90, 278-281, 1992.

The endothelial dysfunction is evaluated by determining the damage the hepatic damage (GPT increase), and the vascular endothelium or cardiovascular damage (blood hypertension) induced by L-NAME administration.

The animals (Long Evans rats, average weight 350-450 g) are divided in groups as herein below described. The group receiving L-NAME is treated for 4 weeks with said compound

dissolved at the concentration of 400 mg/litre in drinking water. The following groups (No. 10 animals for group) are constituted:

A) Control groups:

1° group: treatment: only carrier (physiologic solution),

2° group: treatment: carrier + L-NAME,

B) Groups treated with the drug:

3° group: treatment: carrier + drug,

4° group: treatment: carrier + drug + L-NAME.

The drugs screened in the test are hydrocortisone, desamethasone, prednisolone, chenodeoxycholic acid, ursodesoxycholic acid and the corresponding derivatives according to the present invention.

In those groups of rats treated, respectively, with hydrocortisone, desamethasone, prednisolone and thereof corresponding compounds according to the present invention, the blood-pressure is determined.

In those groups of rats treated, respectively, with ursodesoxycholic acid and chenodeoxycholic acid and thereof corresponding compounds according to the present invention, GPT is determined.

Each drug is administered by intraperitoneal route once a day for 4 weeks.

At the end of the four weeks access to water is prevented and after 24 hours the animals are sacrificed.

Four hours after the last administration the blood-pressure is determined.

Damage to the vascular endothelium is determined, as said by the cardiovascular effects induced by L-NAME (increase of the blood pressure). The hepatic damage is determined by evaluation of the glutamic-pyruvic transaminase (GPT increase) after sacrifice.

Results are reported in Tables I and II. The % blood-pressure and GPT values are referred to the corresponding value found in the animals of the 1st control group. The average value of the blood pressure in this group was of 105 mmHg.

The results obtained show that the steroidal precursors cause hepatic damage (ursodesoxycholic acid and chenodeoxycholic acid) and arterial hypertension (hydrocortisone, desamethasone, prednisolone). GPT and blood pressure values of the treated rats are higher compared both with the corresponding groups treated with drug in the absence of L-NAME and with the controls treated with L-NAME. The products of the invention are instead better tolerated in comparison with the corresponding precursors, even in animals not pretreated with L-NAME.

EXAMPLE F2

Test 4: inhibition of the radical production from DPPH of some substances used to prepare the precursors of B or B1

The method is based on a colorimetric test in which DPPH

(2,2-diphenyl-1-picryl-hydrazyl) is used as the compound-forming radicals (M.S. Nenseter et Al., Atheroscler. Thromb. 15, 1338-1344, 1995).

Solutions in methanol of the tested substances at a final concentration 100 μ M are initially prepared. 0.1 ml of each of these solutions are added to aliquots of 1 ml of a methanol solution 0.1 M of DPPH and then the final volume is brought to 1.5 ml. After having stored the solutions at room temperature away from light for 30 minutes, the absorbance at the wave length of 517 nm is read. It is determined the absorbance decrease with respect to the absorbance of a solution containing the same concentration of DPPH.

The efficacy of the test compound to inhibit the production of radicals, otherwise said antiradical activity, is expressed by the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are, respectively, the absorbance values of the solution containing the test compound together + DPPH and of the solution containing only DPPH.

The compound to be used as precursor of B or B₁ according to the present invention meets test 4 if it inhibits radical production from DPPH in a percent equal to or higher than 50%.

In Table III are reported the results obtained in said test with the following compounds: N-acetylcysteine, cysteine, ferulic acid, (L)-carnosine, gentisic acid, 4-thiazolidin

carboxylic acid and 2-oxo-4-thiazolidincarboxylic acid.

Table III shows the following:

- N-acetylcysteine, cysteine, ferulic acid, (L)-carnosine, gentisic acid meet test 4 since they inhibit the production of radicals induced by DPPH to an extent higher than 50%. Therefore they can be used as precursors of the B compound in the synthesis of the compounds according to the present invention.
- 4-thiazolidin carboxylic acid and the 2-oxo-4-thiazolidin carboxylic acid do not meet test 4 since they do not inhibit radical production from DPPH. Therefore they can be used as precursors of B or B₁ if they meet test 5.

EXAMPLE F3

Test 5: Inhibition of the radical production from Fe^{II} from compounds used as precursors of B, B₁ or C = -T_C-Y-H.

0.1 ml aliquots of 10⁻⁴ M methanolic solutions of 4-thiazolidin carboxylic acid and 2-oxo-4-thiazolidin carboxylic acid are added to test tubes containing an aqueous solution formed by mixing 0.2 ml of 2 mM desoxyribose, 0.4 ml of buffer phosphate pH 7.4 100 mM and 0.1 ml of 1 mM Fe^{II}(NH₄)₂(SO₄)₂ in 2mM HCl. The test tubes are then kept at a temperature of 37°C for one hour. Then in each test tube 0.5 ml of a 2.8% solution in trichloroacetic acid in water and 0.5 ml of an aqueous solution 0.1 M thiobarbituric acid are added in the order. A reference blank is constituted by substituting the above 0.1 ml

aliquots of the test compound methanolic solutions with 0.1 ml of methanol. The test tubes are closed and heated in an oil bath at 100°C for 15 minutes. A pink coloration develops the intensity of which is proportional to the quantity of desoxyribose undergone to radical oxidative degradation. The solutions are cooled at room temperature and their absorbances at 532 nm are read against the blank.

The inhibition induced by the precursor of B or B₁ or C = -T_C-Y-H (wherein the free valence is saturated as above defined) with respect to radical production from Fe^{II} is determined as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound + the iron salt and that of the solution containing only the iron salt.

The results are reported in Table IV, which shows that both acids meet test 5 since they inhibit radical production from Fe^{II} in a percentage higher than 50%. Therefore both 4-thiazolidin carboxylic acid and 2-oxo-4-thiazolidin carboxylic acid can be used as precursors of B, B₁ or C = -T_C-Y-H for obtaining compounds of the present invention.

EXAMPLE F4

Example F1 was repeated with three groups of rats (each group of ten animals), one control group not receiving L-NAME and two groups receiving L-NAME, and i.p. administered as it

follows :

- a. control group (not receiving L-NAME) : the carrier (physiologic solution),
- b. 1st group receiving L-NAME (group b - comparative) administered at the same time with 25 mg/Kg (0.064 mmol/Kg) of dexamethasone + 10.4 mg/Kg (0.064 mmol/Kg) of N-acetylcysteine in the same above carrier,
- c. 2nd group receiving L-NAME (group c) administered with 42.5 mg/Kg (0.064 mmol/Kg) of the dexamethasone derivative according to the invention (ref. ex. 5) in the same above carrier.

In this experiment vascular tolerability, i.e. the rise in blood pressure (vascular damage) was determined in the animals of groups b and c and expressed as percentages to that of the control group a, assumed to be 100 %.

The results are reported in Table V and show that the mixture administered to group b (comparative) induced in the animals an higher blood pressure increase than the compound of the invention (group c).

EXAMPLE F5

Example F1 was repeated with three groups of rats (each group of of ten animals), one control group not receiving L-NAME and two groups receiving L-NAME, and i.p. administered as it follows :

- a. control group (not receiving L-NAME) : the carrier

(physiologic solution),

- b. 1st group receiving L-NAME (group d - comparative) administered at the same time with 100 mg/Kg (0.25 mmoles/Kg) of ursodesoxycholic acid + 49.5 mg/Kg (0.25 mmoles/Kg) of ferulic acid in the same above carrier,
- c. 2nd group receiving L-NAME (group e) administered with 175 mg/Kg (0.25 mmoles/Kg) of the ursodesoxycholic derivative according to the invention (ref. ex. 1) in the same above carrier.

In this experiment hepatic tolerability, i.e. the rise in GPT (hepatic damage) was determined in the animals of groups d and e and expressed as percentages to that of the control group a, assumed to be 100 %.

The results are reported in Table VI and show that the mixture administered to group d (comparative), induced in the animals an higher GPT increase than the compound of the invention (group e).

Table I

Study of vascular tolerability of hydrocortisone, dexamethasone and prednisolone, and of the corresponding derivatives according to the invention, in animals (rats) both not treated and treated with L-NAME. Vascular tolerability is indicated as % variation of the blood pressure (hypertension) with respect to the controls not treated with L-NAME and treated with the only carrier (physiological solution)				
Compound	Animals non treated with L-NAME		Animals treated with L-NAME	
	dose mg/Kg i.p.	Blood pressure variation %	dose mg/Kg i.p.	Blood pressure variation %
carrier	-	100	-	140
hydrocortisone	10	115	5	160
hydrocortisone der. Ex. 4	10	98	5	120
dexamethasone	5	125	25	170
dexamethasone der. Ex. 5	5	103	25	125
prednisolone	10	119	15	165
prednisolone der. Ex. 3	10	102	15	110

Table II

Study of hepatic damage, determined by GPT assay, of chenodeoxycholic acid and ursodesoxycholic acid, and of the corresponding derivatives according to the invention, in animals (rats) both not treated and treated with L-NAME. The % variation of GPT with respect to the controls not treated with L-NAME and treated with the only carrier (physiological solution)				
Compound	animals non treated with L-NAME		Animals treated with L-NAME	
	dose mg/Kg i.p.	GPT var. %	dose mg/Kg i.p.	GPT var. %
carrier	-	100	-	230
chenodeoxycholic acid	100	150	100	350
chenodeoxycholic acid der. Ex. 2	100	105	100	130
ursodesoxycholic acid	100	130	100	276
ursodesoxycholic acid der. Ex. 1	100	103	100	123

Table III

Test 4: Screening of the effectiveness of some substances to inhibit radical production from DPPH.	
Compound	% inhibition radical production from DPPH
Solvent	0
N-acetylcysteine	100
Cysteine	100
Ferulic acid	100
(L)-carnosine	80
Gentisic acid	80
2-oxo-4-thiazolidin carboxylic acid	0
4-thiazolidin carboxylic acid	0

Table IV

Test 5 : study on the effectiveness of the listed substances to inhibit radical production induced by Fe ^{II}	
Compound	% Radical Inhibition from Fe ^{II}
White	0
2-oxo-4-thiazolidin carboxylic acid	100
4-thiazolidin carboxylic acid	100

Table V

Study of vascular tolerability in animals (rats) treated with L-NAME and i.p. administered with a mixture of dexamethasone + N-acetylcysteine and with the derivative of dexamethasone of ex. 5 according to the invention. Vascular tolerability is indicated as % variation of the blood pressure (hypertension) with respect to the controls not treated with L-NAME and treated with the only carrier.		
Compound	dose mg/Kg i.p.	Blood pressure variation %
controls	-	100
group b - comparative dexamethasone (A)+ N-acetyl cysteine (B)	25(A)+10.4(B)	170
group c dexamethasone der. Ex. 5	42.5	125

Table VI

Study of hepatic tolerability in animals (rats) treated with L-NAME and i.p. administered with a mixture of ursodesoxycholic acid + ferulic acid and with the derivative of ursodesoxycholic acid of ex. 1 according to the invention. Hepatic damage is indicated as % variation of GPT with respect to the controls not treated with L-NAME and treated with the only carrier.		
Compound	dose mg/Kg i.p.	GPT variation %
controls	-	100
group d - comparative ursodesoxycholic acid (C)+ ferulic acid (D)	100(C)+49.5(D)	180
group e ursodesoxycholic acid der. ex. 1	175	123

CLAIMS

1. Steroidal compounds or their salts having the following general formulas (I) and (II):



wherein:

s = is an integer equal to 1 or 2, preferably s = 2;

b0 = 0 or 1;

A = R—, wherein R is the steroidal drug radical as defined hereunder,

B = -T_B-X₂-T_{BI}- wherein

T_B and T_{BI} are equal or different;

T_B = (CO) when the reactive function in the precursor steroid is -OH; T_B = X when the reactive function in the precursor steroid is -COOH;

X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl having from 1 to 5 carbon atoms, or a free valence;

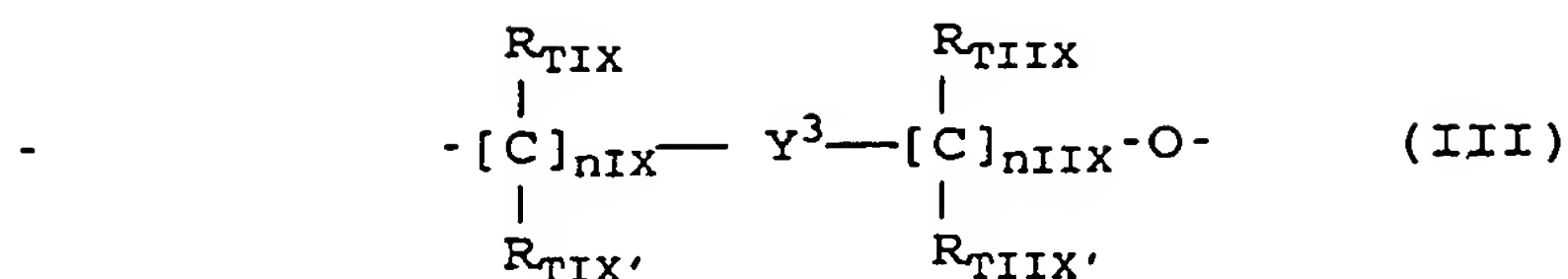
T_{BI} = (CO)_{tx} or (X)_{txx}, wherein tx and txx have the value of 0 or 1; with the proviso that tx = 1 when txx = 0, tx = 0 when txx = 1; X is as above defined;

X₂ is a bivalent bridging group as defined hereunder;

C is the bivalent radical -T_C-Y- wherein

T_C = (CO) when tx = 0, T_C = X when txx = 0, X being as above defined;

Y is:



wherein:

n_{IX} is an integer between 0 and 3, preferably 1;

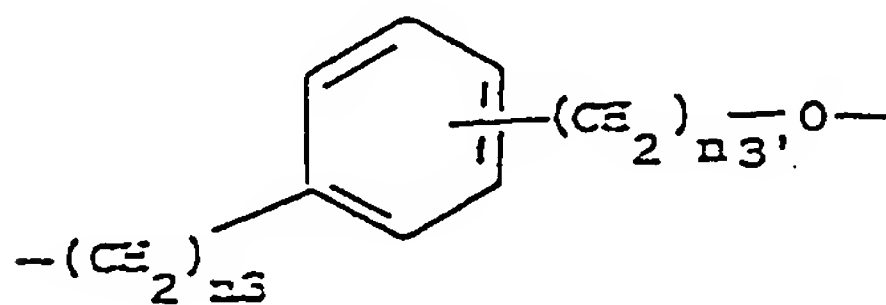
n_{IIX} is an integer between 1 and 3, preferably 1;

R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$, equal to or different from each other are H or a linear or branched C_1 - C_4 alkyl; preferably R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$ are H.

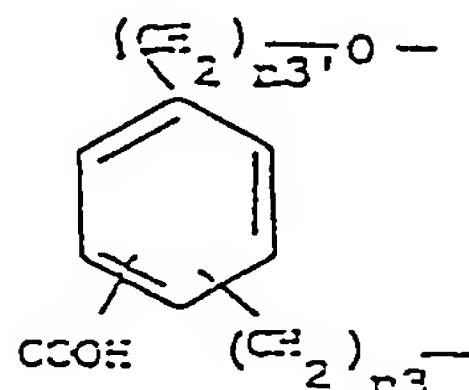
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen atom, said ring having 5 or 6 atoms,

or Y is Y_0 , selected from the following:

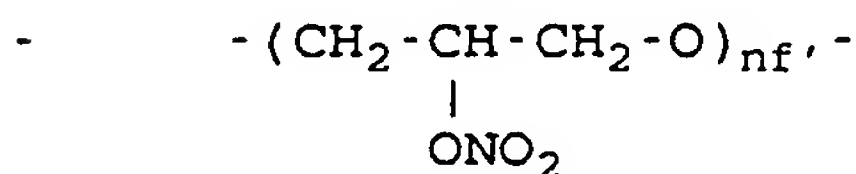
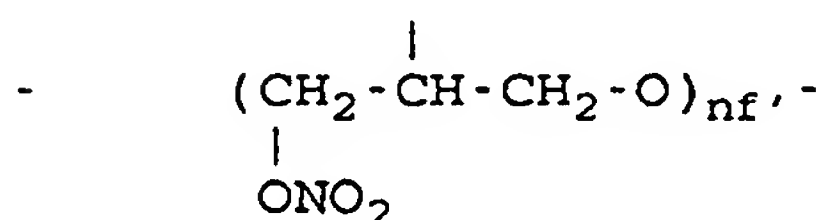
- an alkyleneoxy group $R'O$ wherein R' is linear or when possible branched C_1 - C_{20} , preferably having from 1 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylenic ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type, R' being as above defined; or



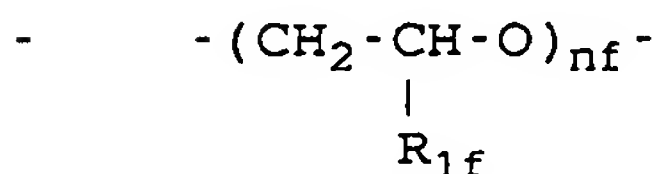
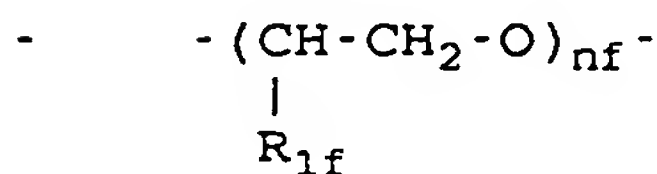
wherein n_3 is an integer from 0 to 3 and n_3' is an integer from 1 to 3;



wherein n_3 and n_3' have the above mentioned meaning



wherein n_f' is an integer from 1 to 6 preferably from 1 to 4;

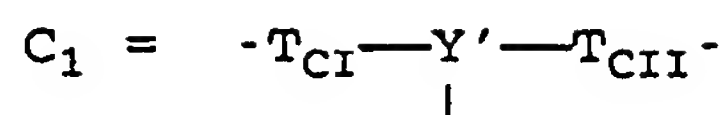


wherein $\text{R}_{1f} = \text{H}, \text{CH}_3$ and n_f is an integer from 1 to 6; preferably from 1 to 4;

preferably $\text{Y} = -\text{Y}_0 = \text{R}'\text{O}-$ wherein R' is as above defined; preferably R' is a $\text{C}_1\text{-C}_6$ alkyl;



wherein:



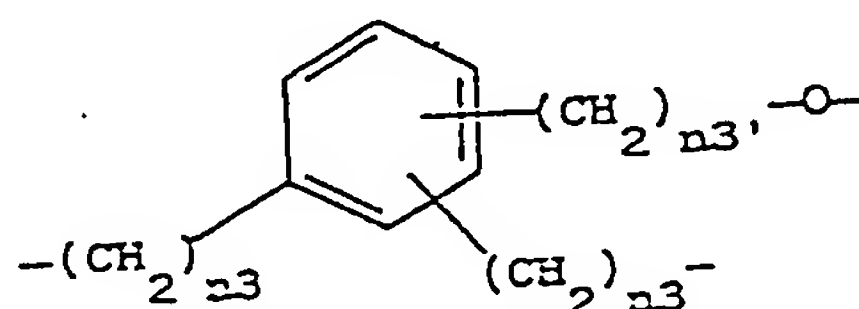
wherein T_{CI} and T_{CII} are equal or different,

$T_{CI} = (CO)$ when the reactive function of the precursor steroid is $-OH$, $T_{CI} = X$ when the reactive function of the precursor steroid is $-COOH$, X being as above defined;

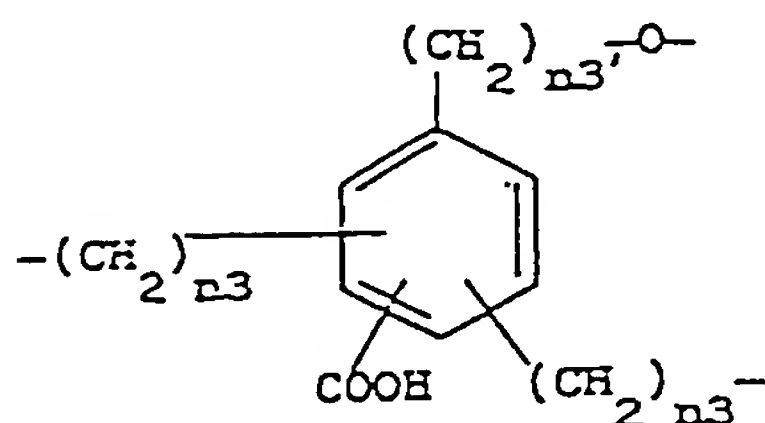
$T_{CII} = (CO)_{tI}$ or $(X)_{tII}$, wherein tI and tII have the 0 or 1 value; with the proviso that $tI = 1$ when $tII = 0$; $tI = 0$ when $tII = 1$; X is as above defined;

Y' is as Y above defined, but with three free valences instead of two, preferably selected from the following:

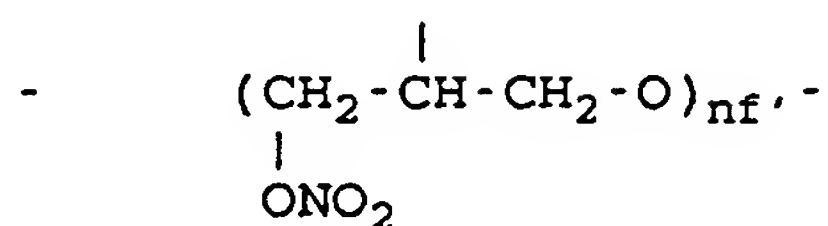
- a $-R'O-$ group wherein R' is C_1-20 linear or branched, preferably having from 1 to 6 carbon atoms, or a saturated ring having from 5 to 7 carbon atoms, optionally substituted; or



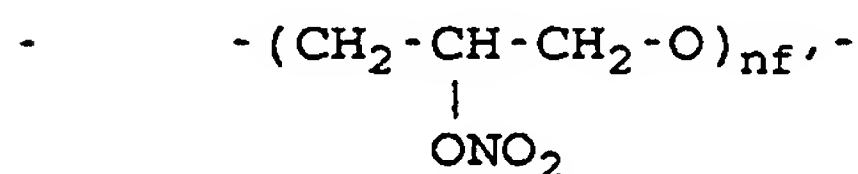
wherein $n3$ is an integer from 0 to 3 and $n3'$ is an integer from 1 to 3;



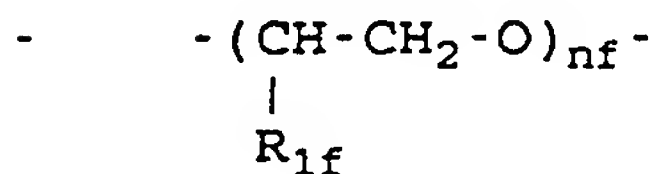
wherein n_3 and n_3' have the above mentioned meaning;



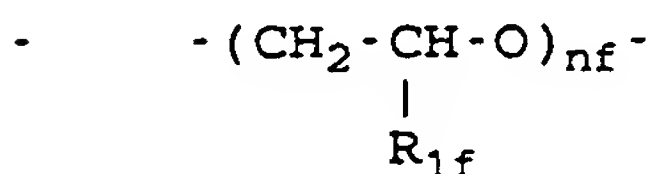
wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein n_f' is an integer from 1 to 6 preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein $\text{R}_{1f} = \text{H}, \text{CH}_3$ and n_f is an integer from 1 to 6; preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;

preferably $\text{Y}' = - \text{R}'\text{O}-$ wherein R' is a linear or branched $\text{C}_2 - \text{C}_4$, the oxygen which in Y' is covalently linked to the $-\text{N}(\text{O})_s$ group finds at the end of the free bond indicated in C_1 formula;

or $\text{Y}' = \text{Y}_0$ as defined in (I) but with three free

valences instead of 2;

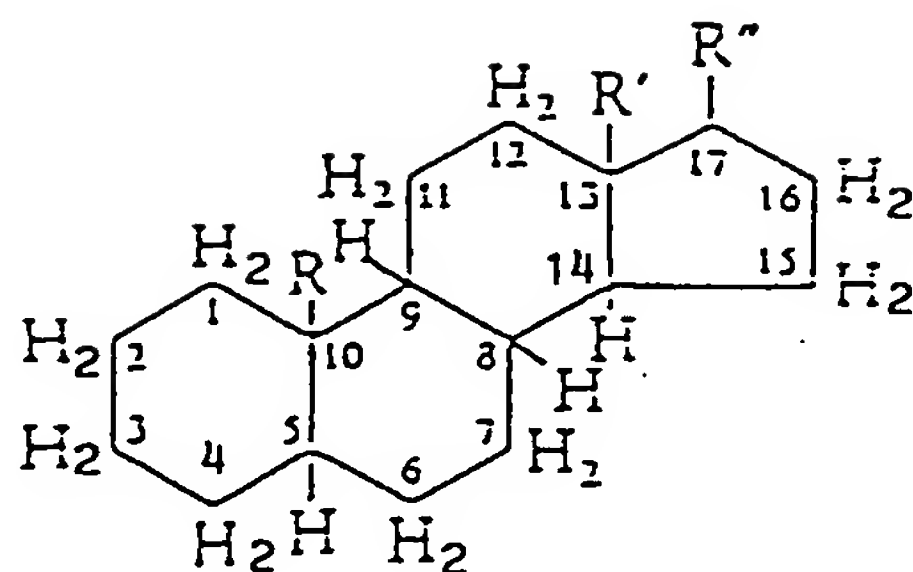


wherein X_{2a} is a monovalent radical,

$T_{BII} = (CO)$ when $tI = 0$, $T_{BII} = X$ when $tII = 0$, X being as above defined;

- X_2 , bivalent radical is such that the corresponding B precursor: $-T_B-X_2-T_{BI}$ meets test 4 or test 5, precursor in which the T_B and T_{BI} free valences are each saturated with OZ, with Z or with $-Z^I-N-Z^{II}$, Z^I and Z^{II} being equal or different and have the Z values as above defined, depending on whether T_B and/or $T_{BI} = CO$ or X, in connection with the values of t, t', tx and txx;
- the C precursor when $b0 = 0$ is of $-T_C-Y-H$ type wherein the T_C free valence is saturated with OZ, Z, or with $-Z^I-N-Z^{II}$, Z^I and Z^{II} being as above defined, meets test 5;
- X_{2a} monovalent radical, such that the corresponding precursor of B_1 $-T_{BII}-X_{2a}$ meets test 4 or test 5, precursor wherein the T_{BII} free valence is saturated with OZ or with Z or with $-Z^I-N-Z^{II}$, Z^I and Z^{II} being equal or different and having the Z values as above defined, depending on whether $T_{BII} = CO$ or X, in connection with the tI and tII values;

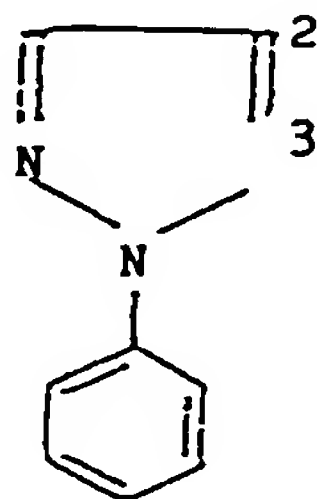
A = R- has the following structure:



wherein in substitution of the hydrogens of the CH groups or of the two hydrogens of the CH₂ groups mentioned in the general formula, the following substituents can be present:

in position 1-2: there may be a double bond;

in position 2-3: there may be the following substituent:



in position 2: there may be Cl, Br;

in position 3: there may be CO, -O-CH₂-CH₂-Cl, OH;

in position 3-4: there may be a double bond;

in position 4-5: there may be a double bond;

in position 5-6: there may be a double bond;

in position 5-10: there may be a double bond;

in position 6: there may be Cl, F, CH₃, -CHO;

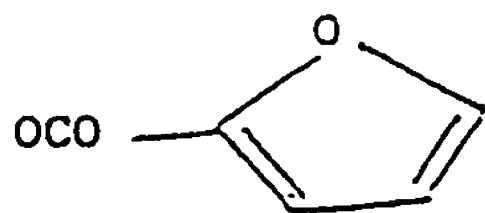
in position 7: there may be Cl, OH;

in position 9: there may be Cl, F;

in position 11: there may be OH, CO, Cl, CH₃;

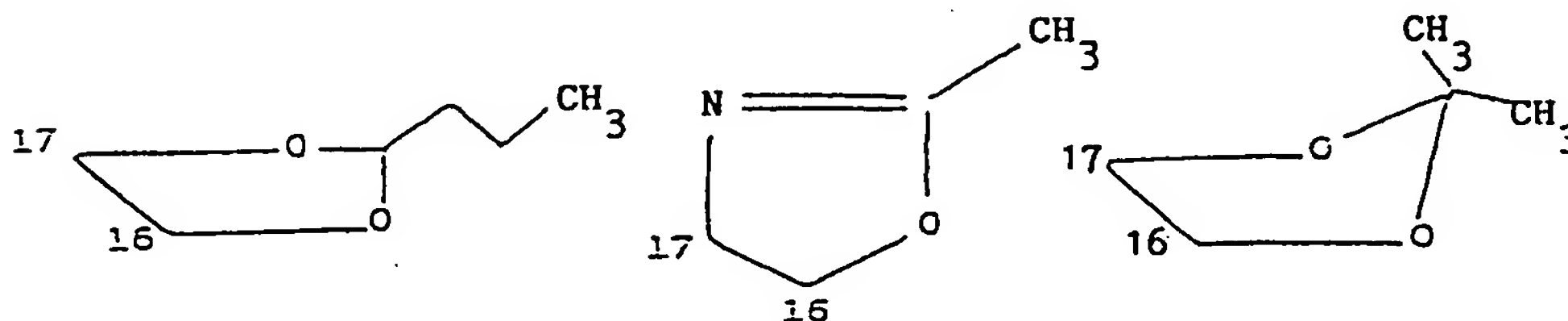
in position 16: there may be CH₃, OH, =CH₂;

in position 17: there may be OH, CH₃, OCO(O)_{ua}(CH₂)_{va}CH₃,
C≡CH or



wherein ua is an integer equal to 0 or 1, va is an integer from 0 to 4;

in position 16-17: there may be the following groups:

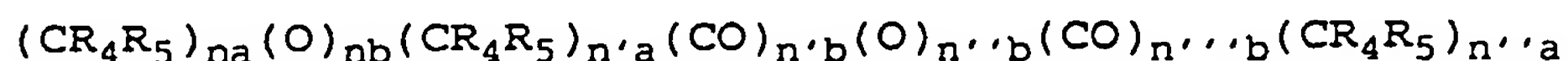


R and R', equal to or different from each other, can be hydrogen or linear or branched alkyls from 1 to 4 carbon atoms, preferably R = R' = CH₃;

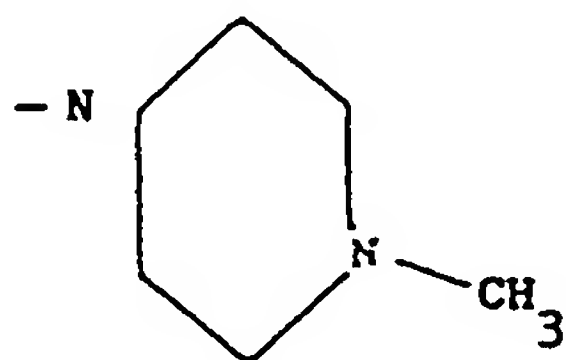
R" is $-(CO-L)_t-(L)_{t2}-(X_0^I)_{t1}-$

wherein t, t1 and t2 are integers equal to or different from each other, equal to 0 or 1, with the proviso that when t = 0 t2 = 1 and when t = 1 t2 = 0, and that t and t1, or t2 and t1, cannot contemporaneously be equal to 0 when A does not contain -OH groups;

the bivalent bridging group L is selected from:



wherein n_a , n'_a , and n''_a , equal to or different from each other, are integers from 0 to 6, preferably 1-3; n_b , n'_b , n''_b and n'''_b , equal to or different from each other, are integers equal to 0 or 1; R_4 , R_5 , equal to or different from each other, are selected from H, linear or branched alkyl from 1 to 5 carbon atoms, preferably from 1 to 3; X_0^I is X as above defined, but R_{1c} is a linear or branched alkyl from 1 to 10 carbon atoms, or equal to X_2^I wherein X_2^I is equal to OH, CH_3 , Cl, $N(-CH_2-CH_3)_2$, SCH_2F , SH, or



wherein test 4, which must be met by the precursors of B or B_1 with the free valences saturated as above defined, is the following: it is an analytical determination carried out by adding portions of methanol solutions of the precursor of B or B_1 at a 10^{-4} M concentration, to a methanol solution of DPPH (2,2-diphenyl-1-picryl hydrazyl - free radical); after having maintained the solution at room temperature away from light for 30 minutes, it is read the absorbance at the wave length of 517 nm of the test solution and of a solution containing only DPPH in the same amount as in the

test solution; and then the inhibition induced by the precursor towards radical production by DPPH is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the test compound + DPPH and that of the solution containing only DPPH; test 4 is met by B or B_1 precursor compounds if the % inhibition as above defined is higher than or equal to 50%;

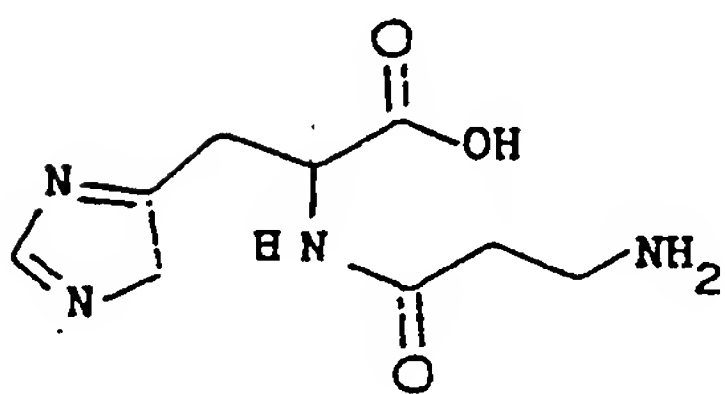
wherein test 5 is an analytical determination carried out by adding aliquots of 10^{-4} M methanol solutions of the precursor of B or B_1 or of $C = -T_c-Y-H$, having the free valence saturated as above indicated, to a solution formed by admixing a 2 mM solution of desoxyribose in water with 100 mM of phosphate buffer and 1 mM of the salt $Fe^{II}(NH_4)_2(SO_4)_2$; after having thermostatted the solution at 37°C for one hour, aliquots of aqueous solutions of trichloroacetic acid 2.8% and of thiobarbituric acid 0.5 M are added, in the order, heating is effected at 100°C for 15 minutes and the absorbance of the tested solutions is then read at 532 nm; the inhibition induced by the precursor of B or B_1 or $C = -T_c-Y-H$ with respect to radical production by Fe^{II} is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

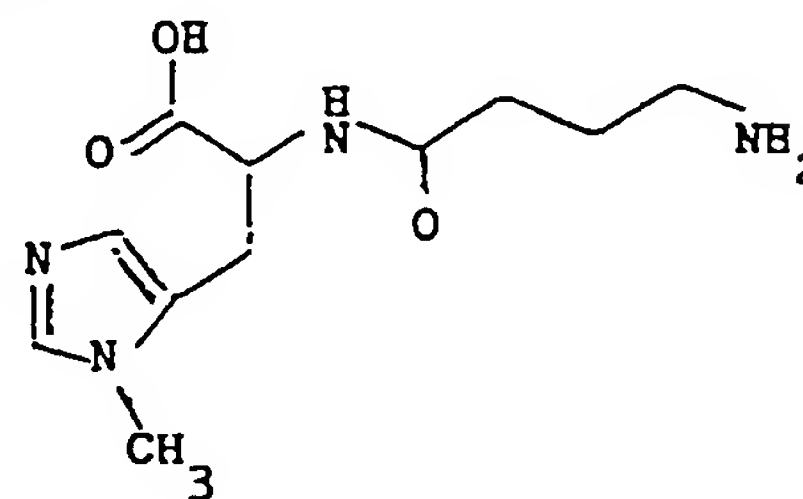
wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound and the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage as above defined of the precursor of B or B_1 or $C = -T_c-Y-H$ is higher than or equal to 50%; provided that in the compounds of formula (I) are excluded the drugs with $A = R-$ when $b_0 = 0$ and $C = -T_c-Y_0-$ wherein the free valence of Y_0 is saturated as indicated above, $s = 1$ or 2.

2. Compounds according to claim 1, wherein the precursor compound of B or B_1 which meets test 4, is selected in the following classes:

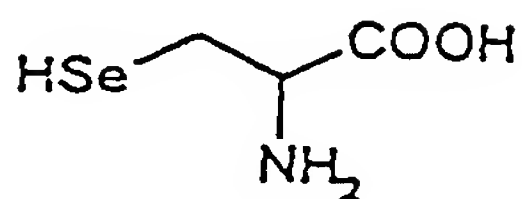
- Aminoacids, selected from the following: L-carnosine (formula CI), anserine (CII), selenocysteine (CIII), selenomethionine (CIV), penicillamine (CV), N-acetyl-penicillamine (CVI), cysteine (CVII), N-acetyl-cysteine (CVIII), glutathione (CIX) or its esters, preferably ethyl or isopropyl ester:



(CI)



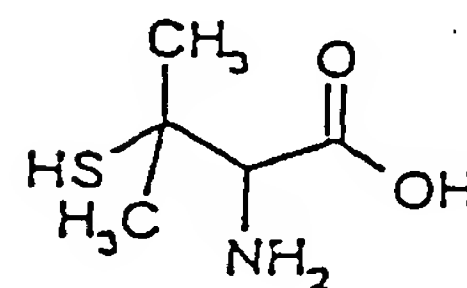
(CII)



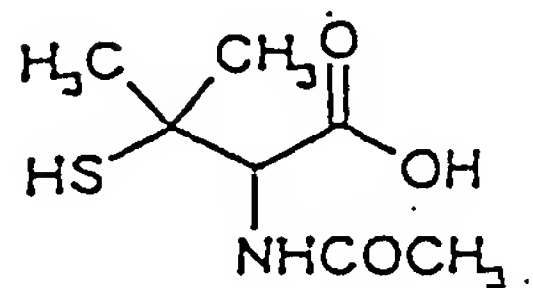
(CIII)



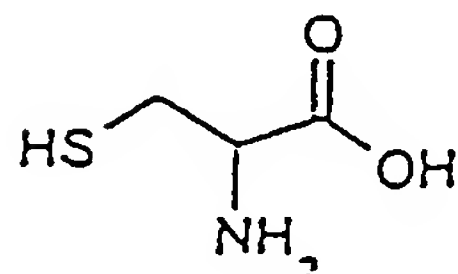
(CIV)



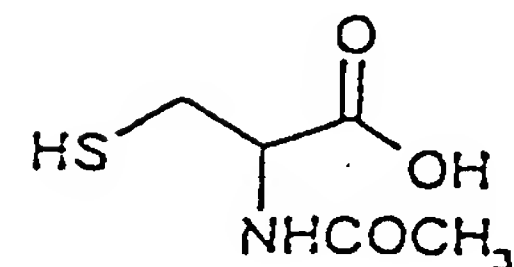
(CV)



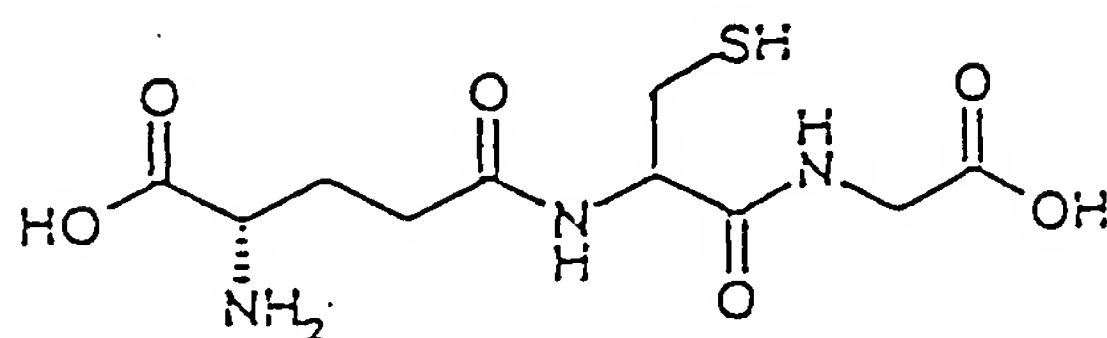
(CVI)



(CVII)

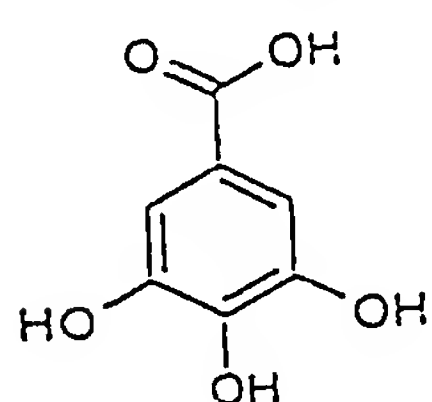


(CVIII)

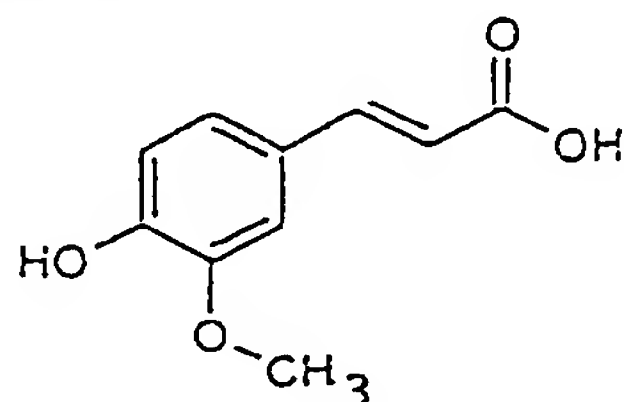


(CIX)

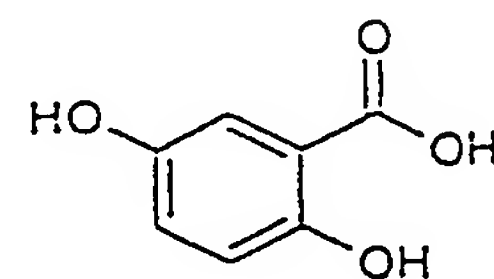
- hydroxyacids, selected from the following: gallic acid (formula DI), ferulic acid (DII), gentisic acid (DIII), citric acid (DIV), caffeic acid (DV), hydro caffeic acid (DVI), p-coumaric acid (DVII), vanillic acid (DVIII), chlorogenic acid (DIX), kynurenic acid (DX), syringic acid (DXI):



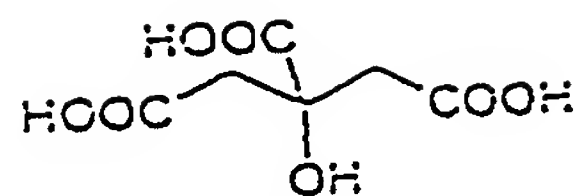
(DI)



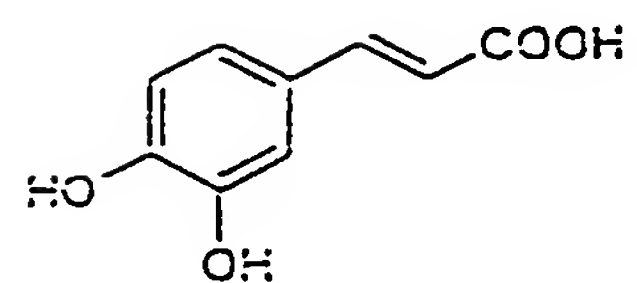
(DII)



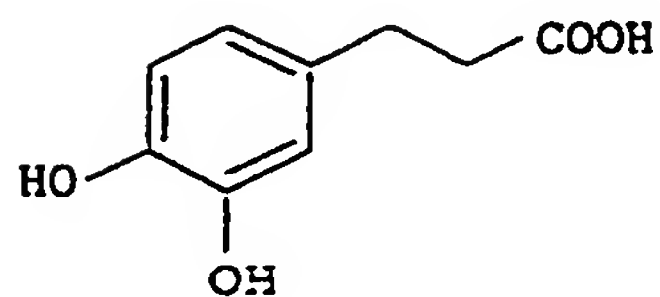
(DIII)



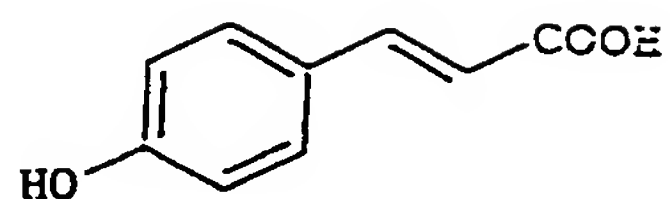
(DIV)



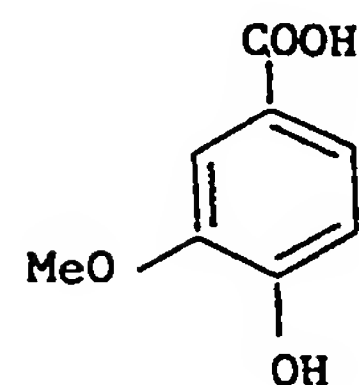
(DV)



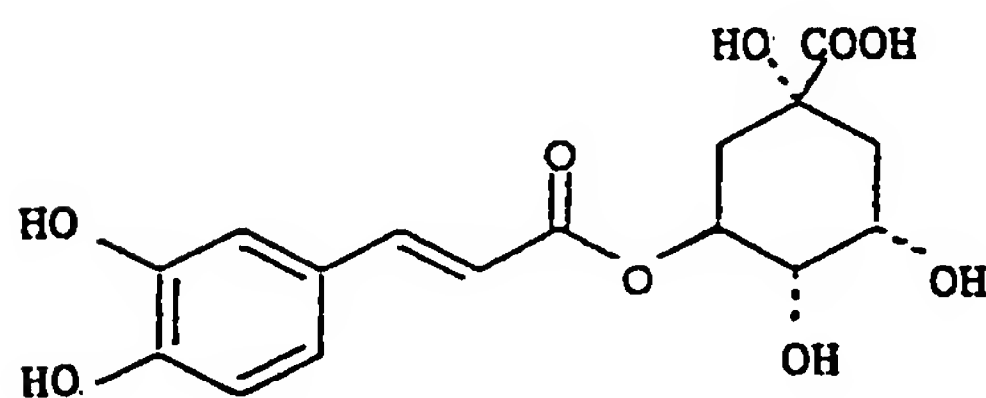
(DVI)



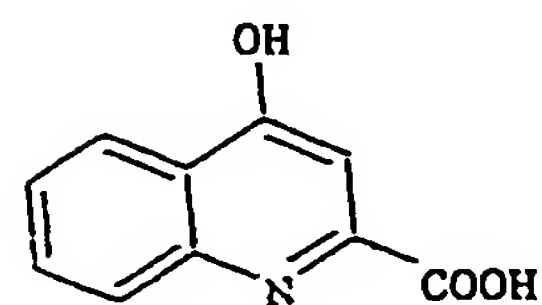
(DVII)



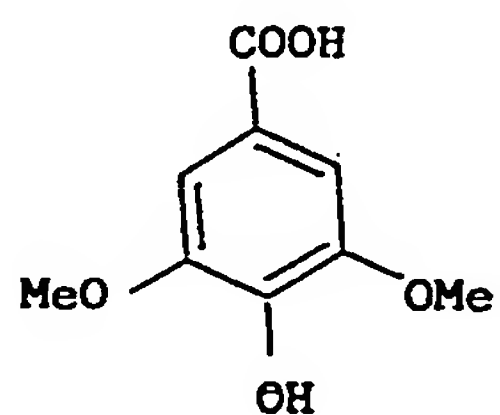
(DVIII)



(DIX)



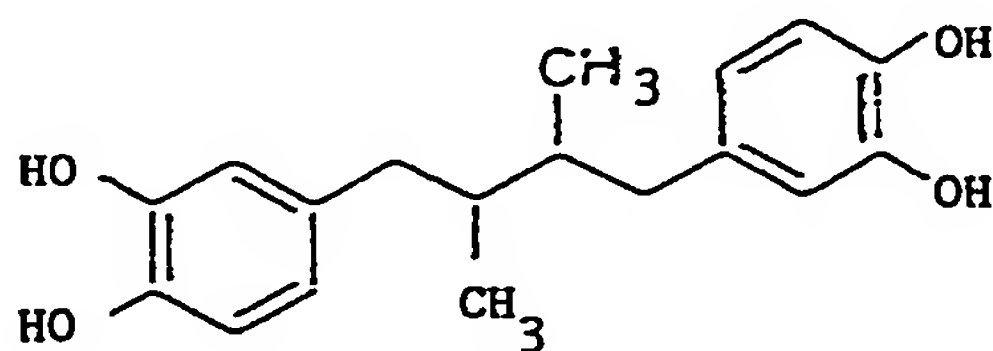
(DX)



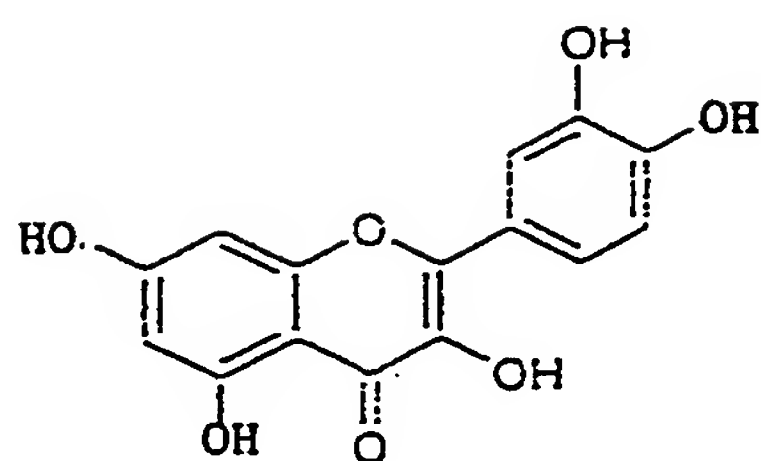
(DXI)

- Aromatic and heterocyclic mono- and polyalcohols,
selected from the following: nordihydroguaiaretic

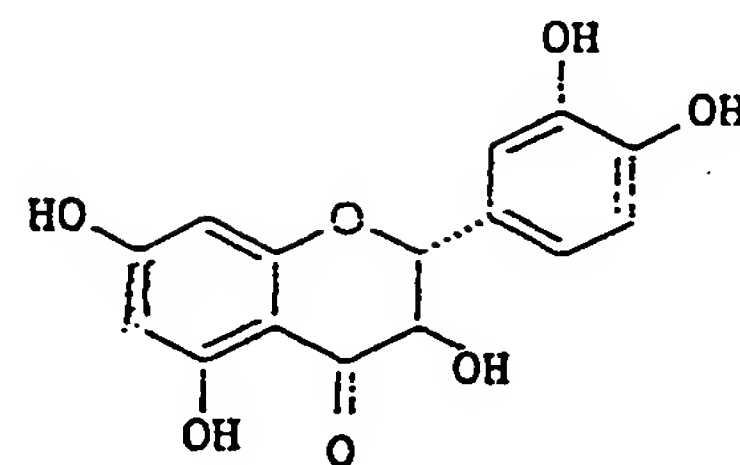
acid (EI), quercetin (EII), catechin (EIII), kaempferol (EIV), sulphurethyne (EV), ascorbic acid (EVI), isoascorbic acid (EVII), hydroquinone (EVIII), gossypol (EIX), reductic acid (EX), methoxyhydroquinone (EXI), hydroxyhydroquinone (EXII), propyl gallate (EXIII), saccharose (EXIV), vitamin E (EXV), vitamin A (EXVI), 8-quinolol (EXVII), 3-tert-butyl-4-hydroxyanisole (EXVIII), 3-hydroxyflavone (EXIX), 3,5-tert-butyl-p-hydroxytoluene (EXX), p-tert-butyl phenol (EXXI), timolol (EXXII), xibornol (EXXIII), 3,5-di-ter-butyl-4-hydroxybenzyl-thioglycolate (EXXIV), 4'-hydroxybutyranilide (EXXV), guaiacol (EXXVI), tocol (EXXVII), isoeugenol (EXXVIII), eugenol (EXXIX), piperonyl alcohol (EXXX), allopurinol (EXXXI), conyferyl alcohol (EXXXII), 4-hydroxyphenetyl alcohol (EXXXIII), p-coumaric alcohol (EXXXIV), curcumin (EXXXV):



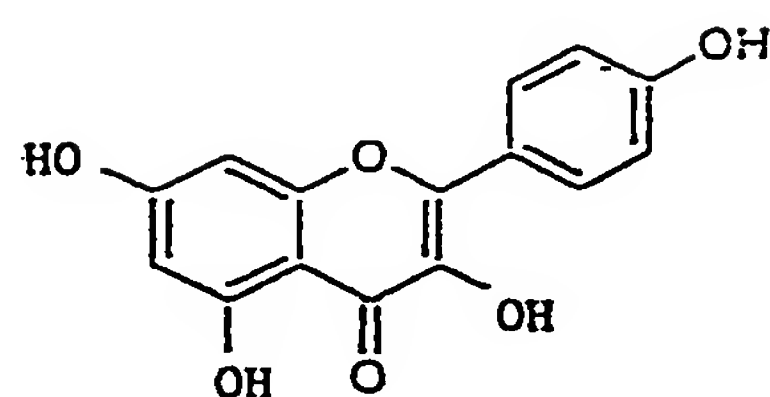
(EI)



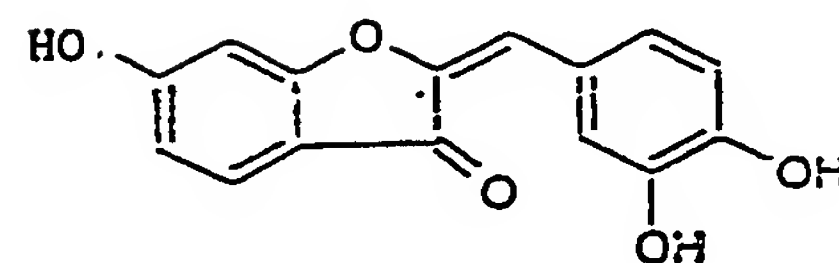
(EII)



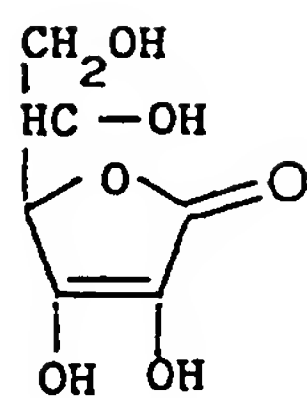
(EIII)



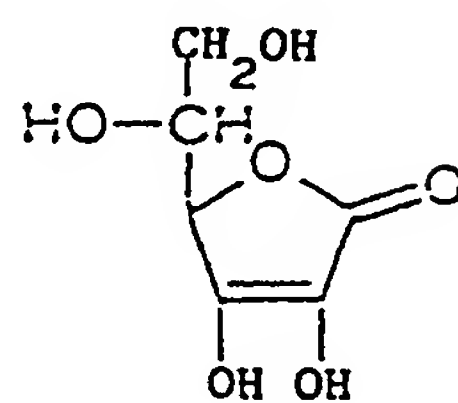
(EIV)



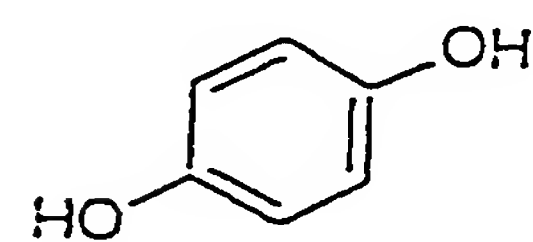
(EV)



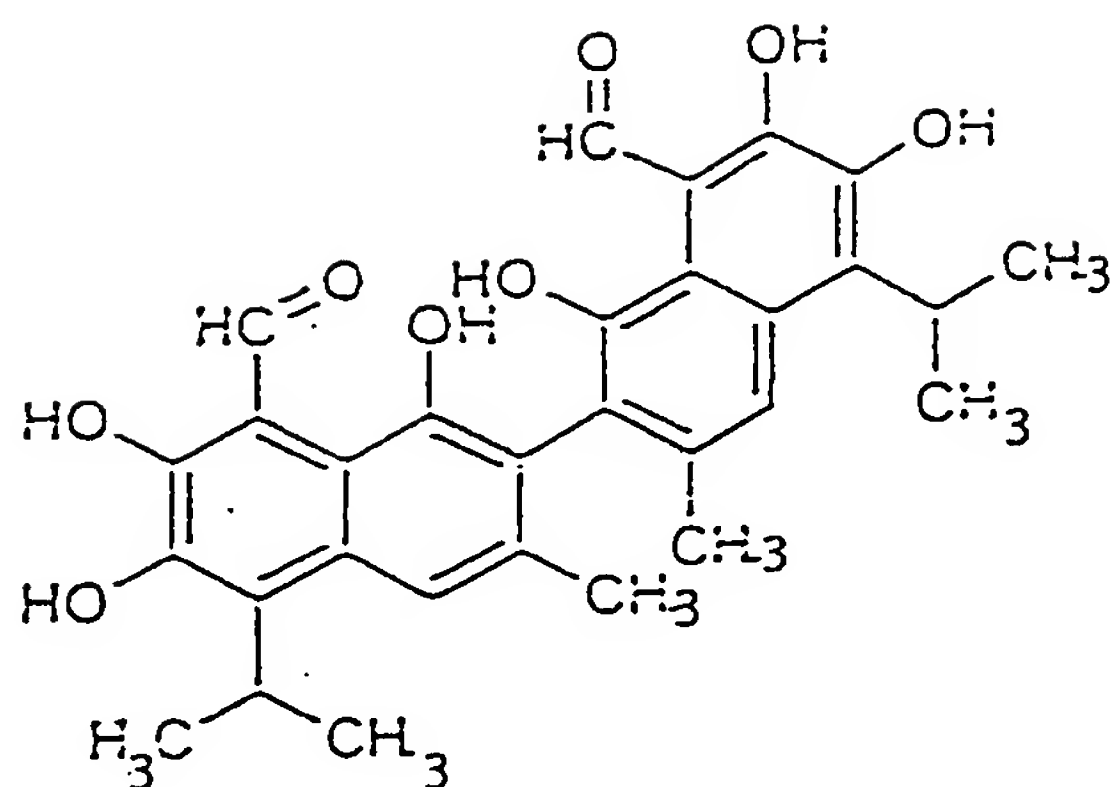
(EVI)



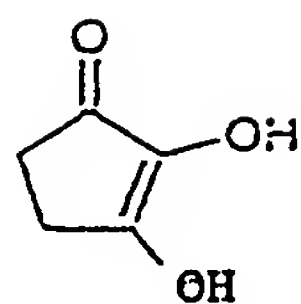
(EVII)



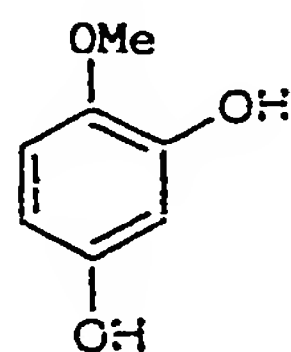
(EVIII)



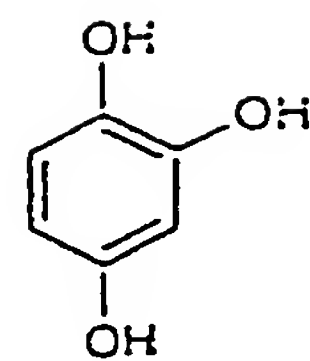
(EIX)



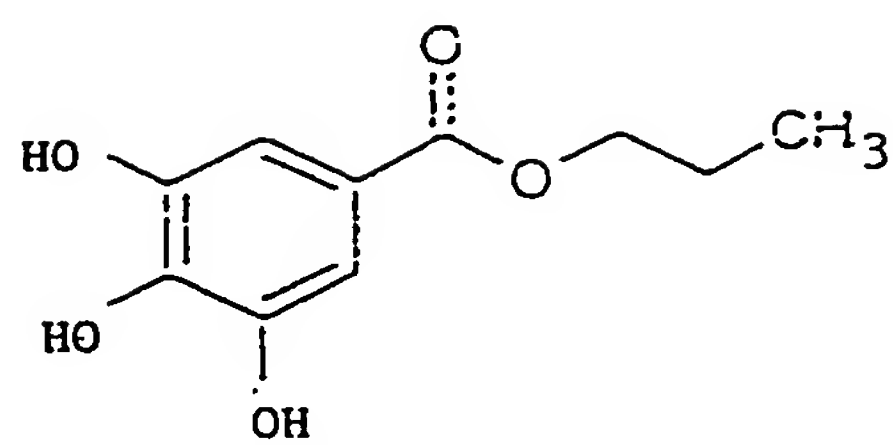
(EX)



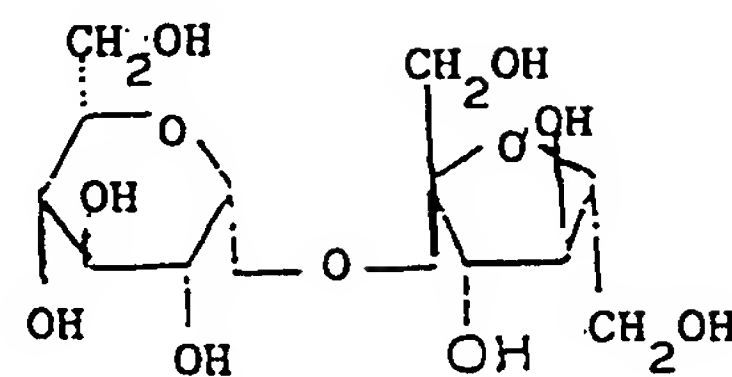
(EXI)



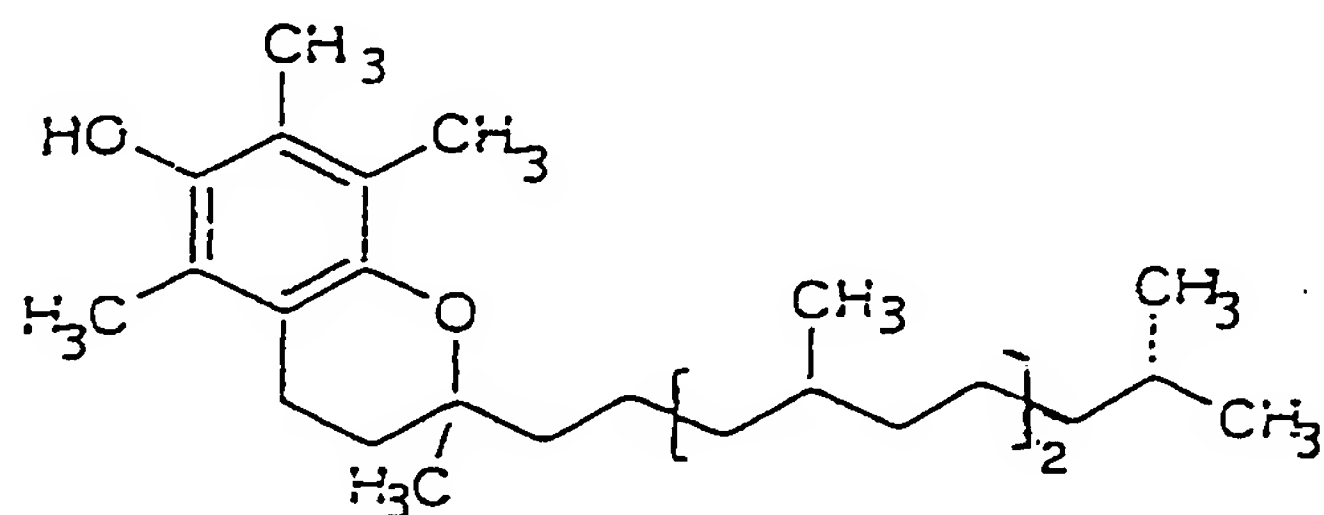
(EXII)



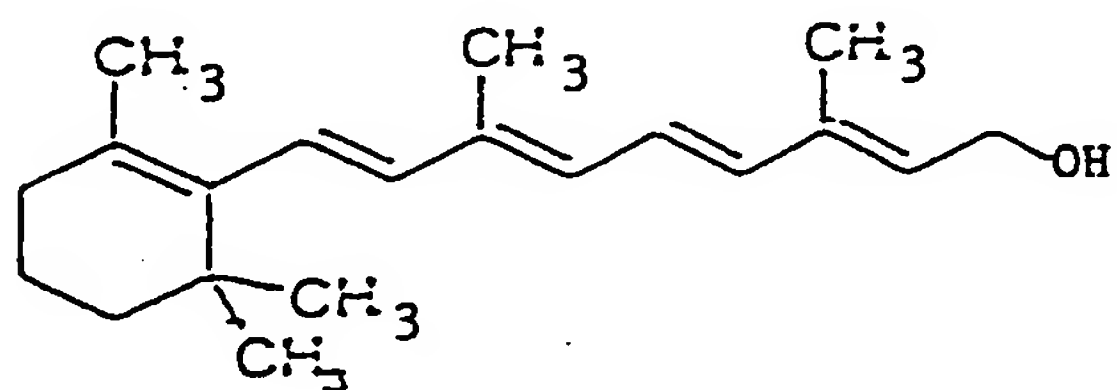
(EXIII)



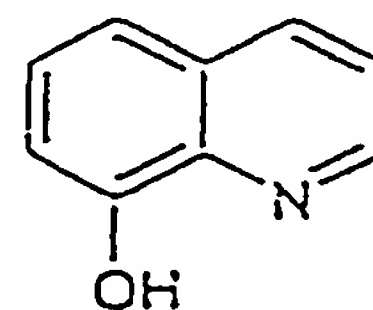
(EXIV)



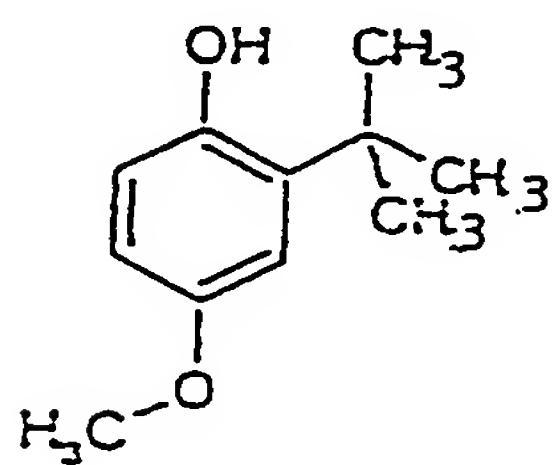
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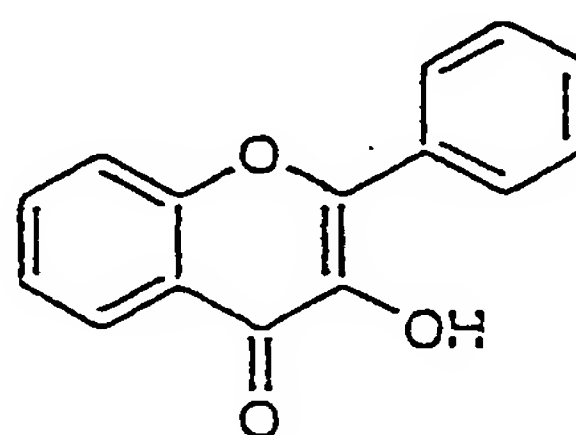
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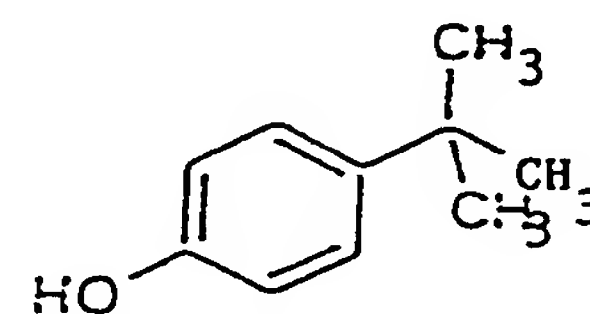
(EXVII)



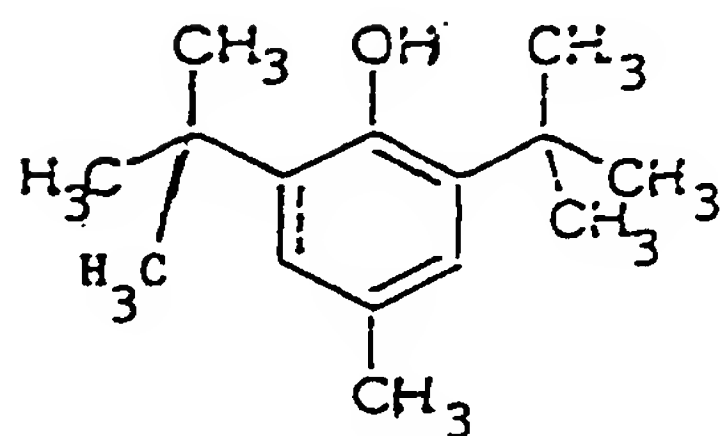
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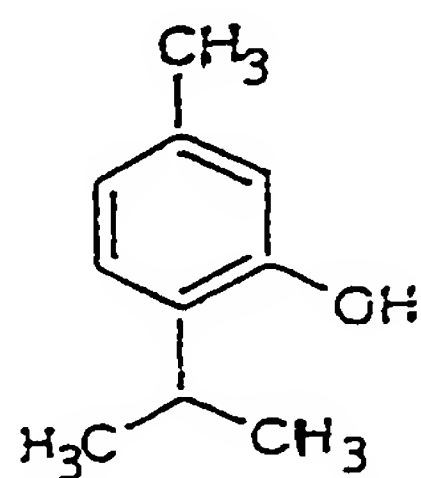
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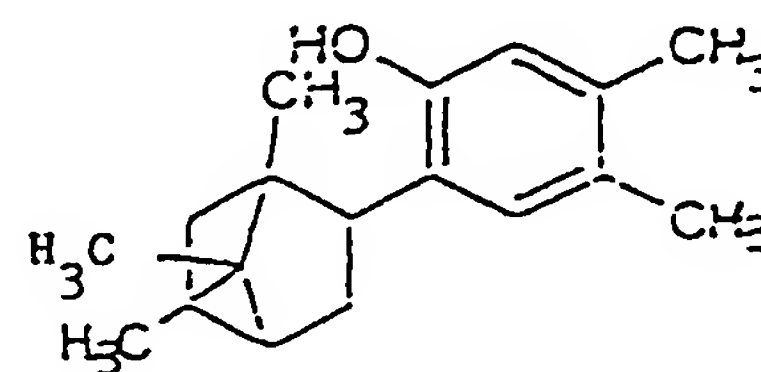
(EXXI)



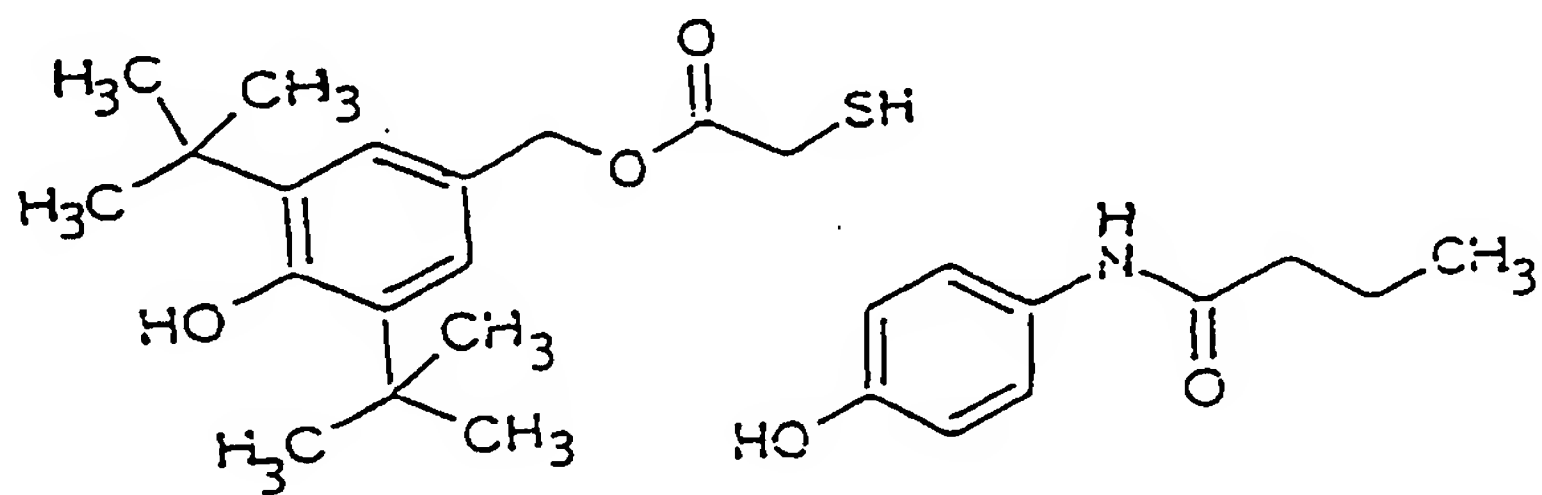
(EXX)



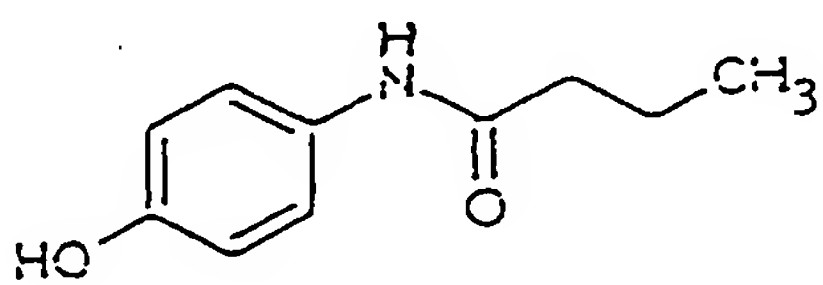
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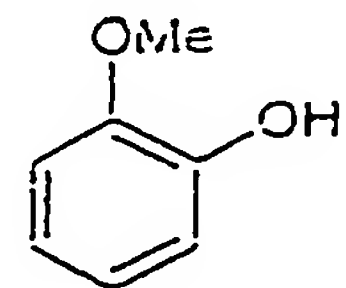
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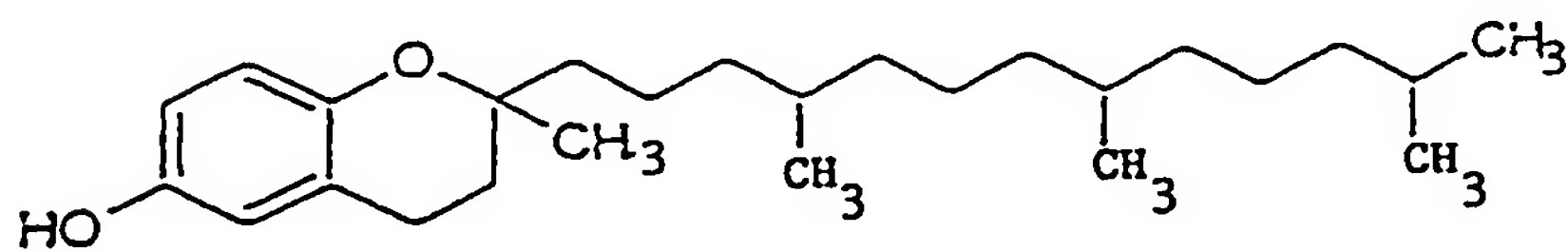
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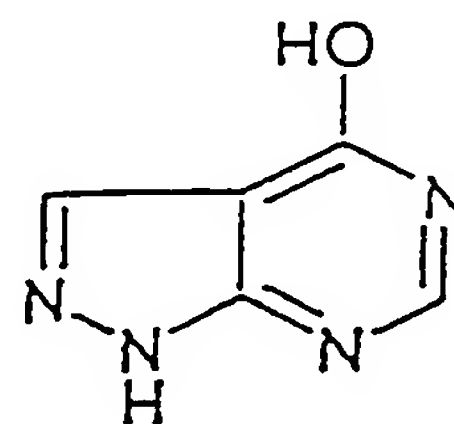
(EXXV)



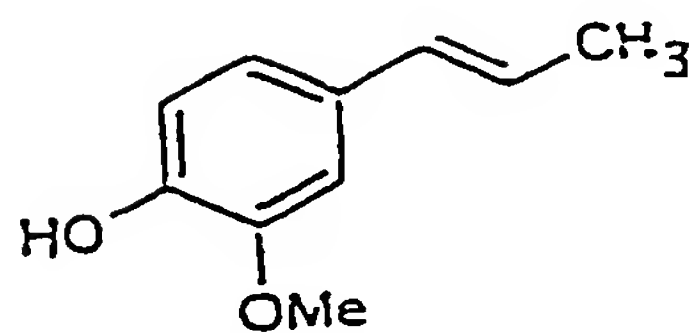
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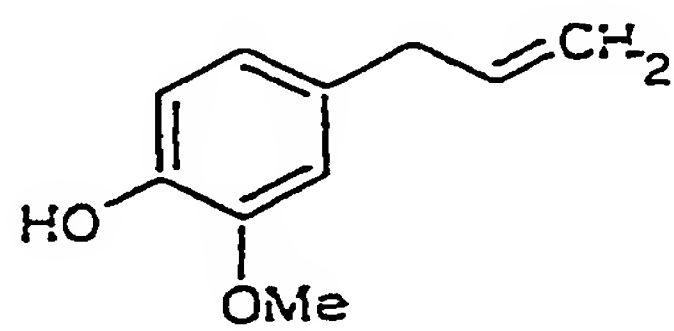
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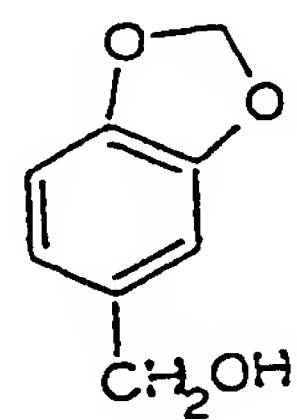
(EXXXI)



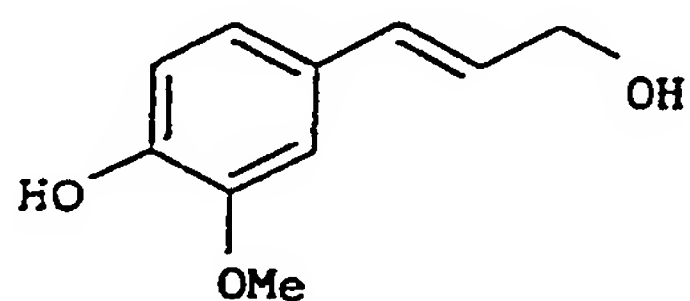
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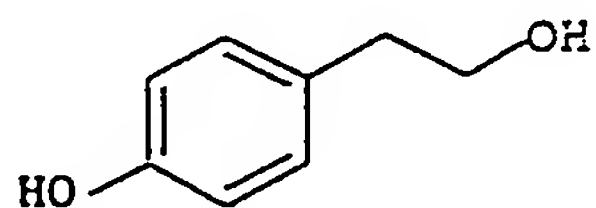
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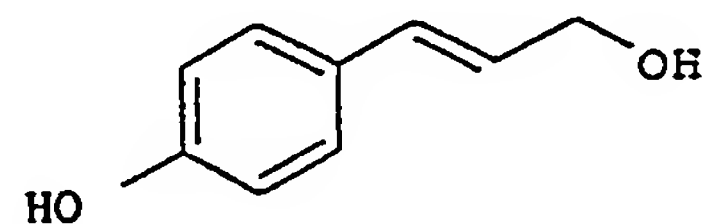
(EXXX)



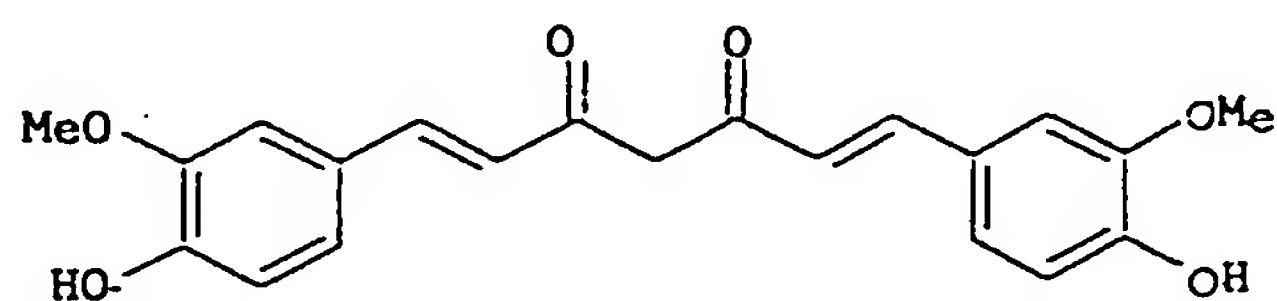
(EXXXII)



(EXXXIII)

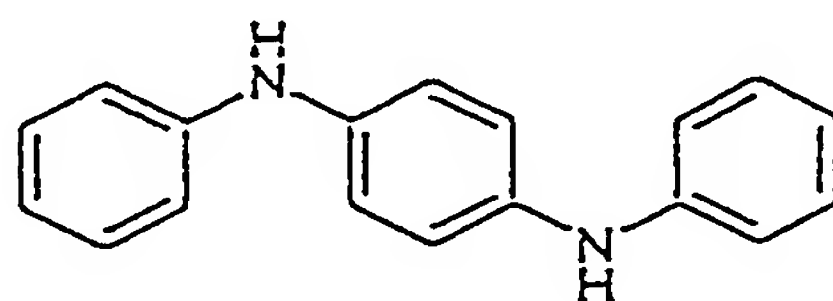


(EXXXIV)

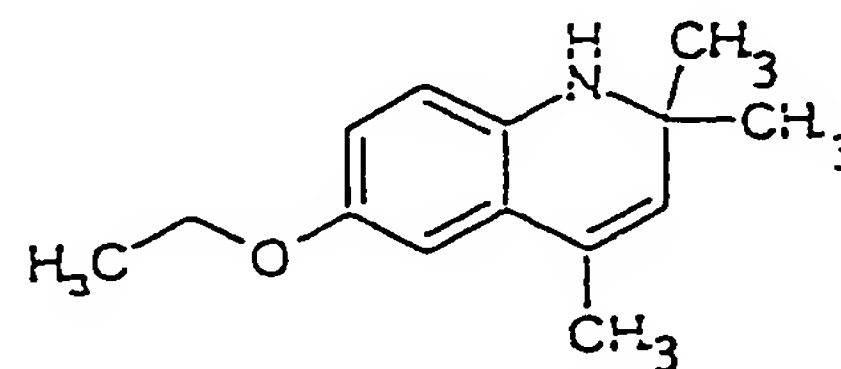


(EXXXV)

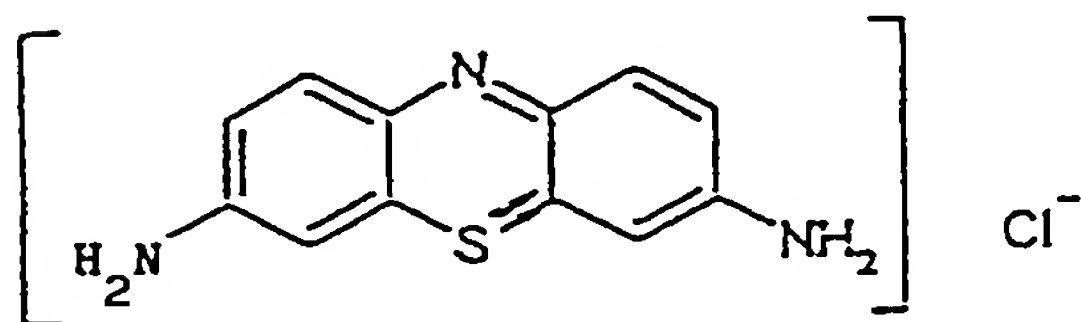
- aromatic and heterocyclic amines, selected from the following: N, N'-diphenyl-p-phenylenediamine (MI), ethoxyquin (MII), thionine (MIII), hydroxyurea (M-IV):



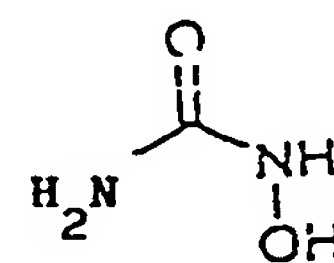
(MI)



(MII)

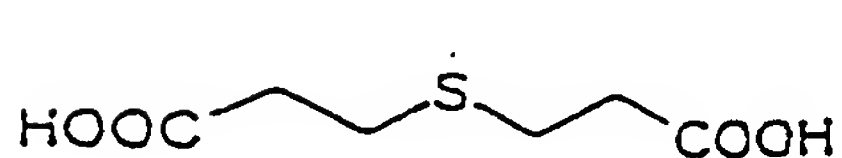


(MIII)

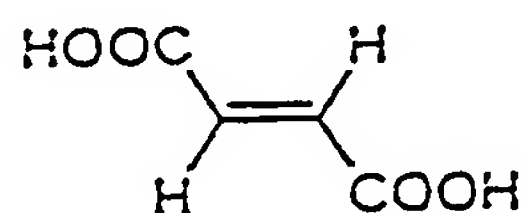


(MIV)

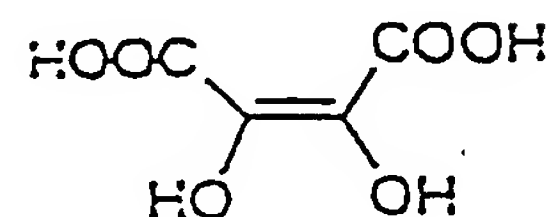
- Compounds containing at least a free acid function, selected from the following: 3,3'-thiodipropionic acid (NI), fumaric acid (NII), dihydroxymaleic acid (NIII), thiocctic acid (NIV), edetic acid (NV), bilirubin (NVI), 3,4-methylenedioxcinnamic acid (NVI-I), piperonylic acid (NVIII):



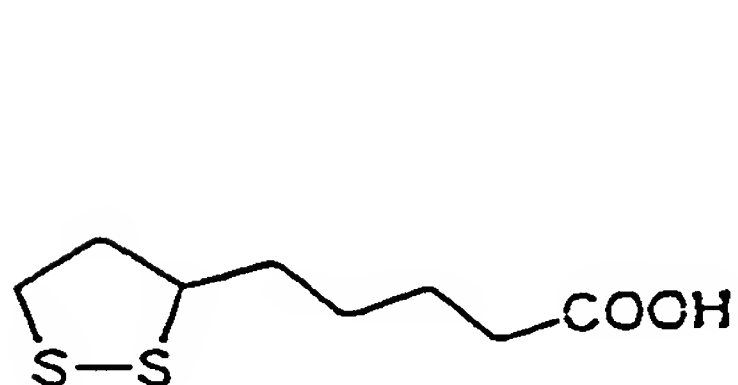
(NI)



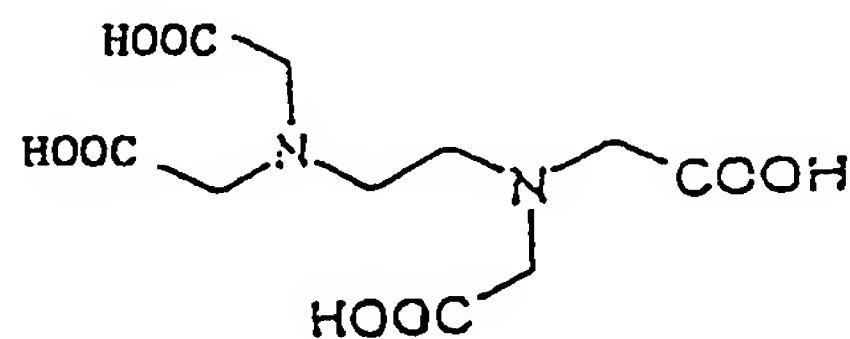
(NII)



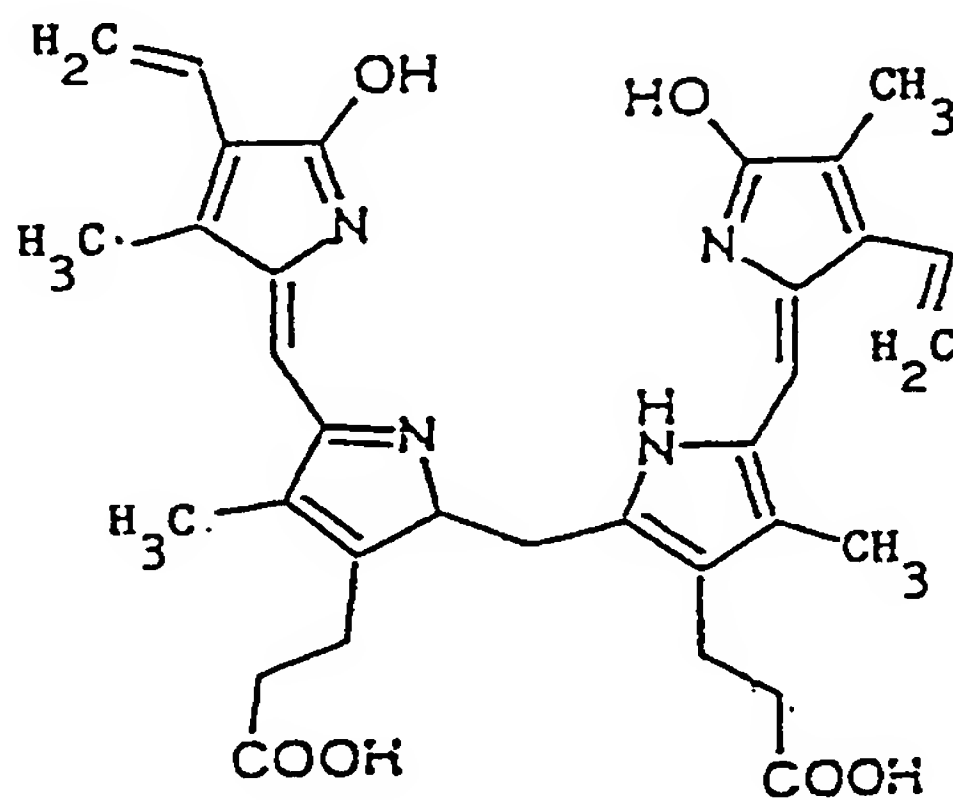
(NIII)



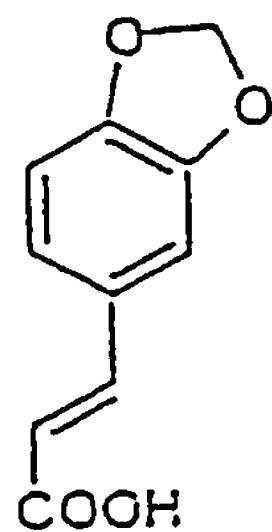
(NIV)



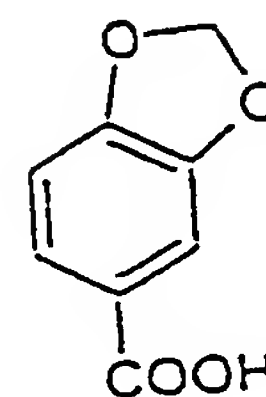
(NV)



(NVI)



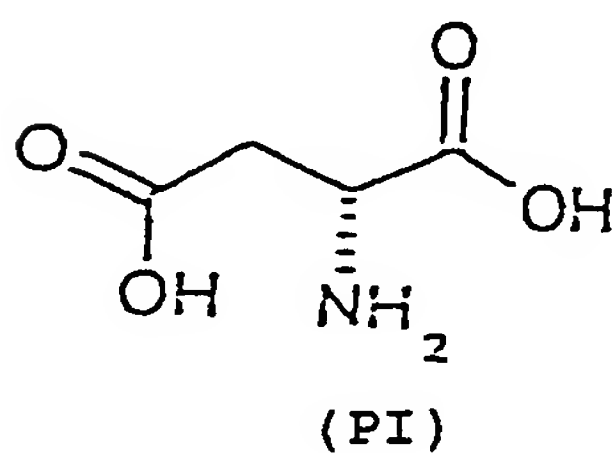
(NVII)



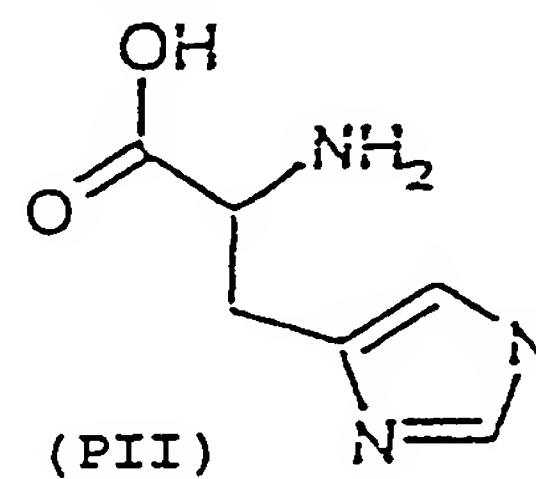
(NVIII)

3. Compounds according to claim 1 wherein the precursor compound of B or B₁ meeting test 5 is selected from the following:

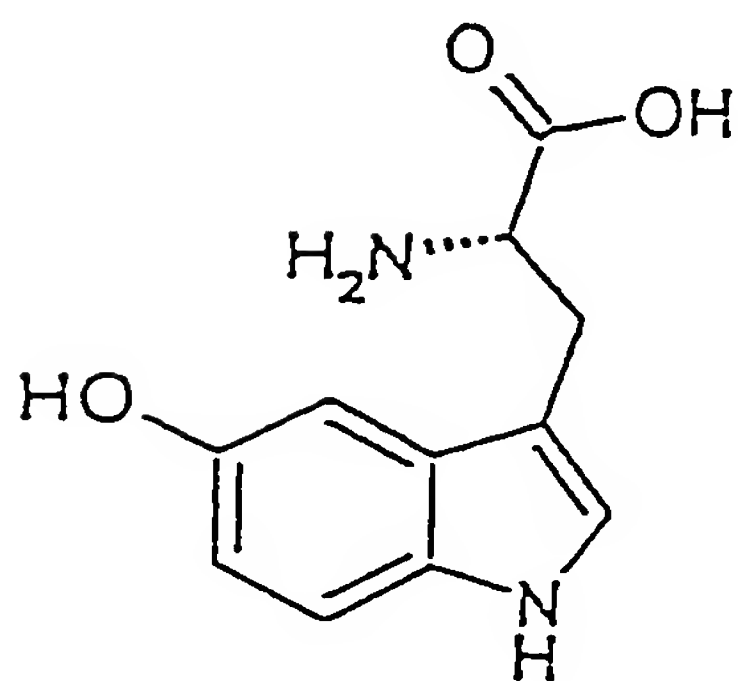
- Aminoacids: aspartic acid (PI), histidine (PII), 5-hydroxytryptophan (PIII), 4-thiazolidincarboxylic acid (PIV), 2-oxo-4-thiazolidincarboxylic acid (PV)



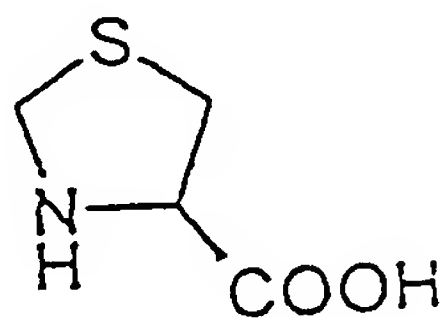
(PI)



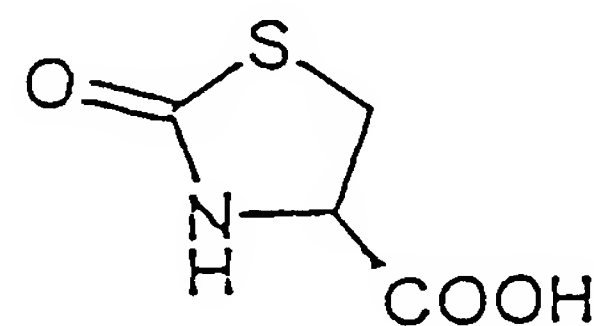
(PII)



(PIII)

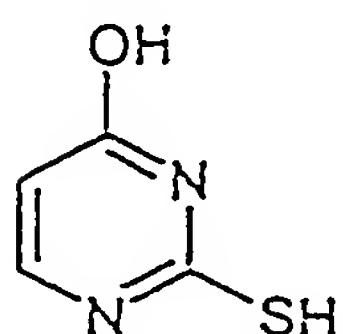


(PIV)



(PV)

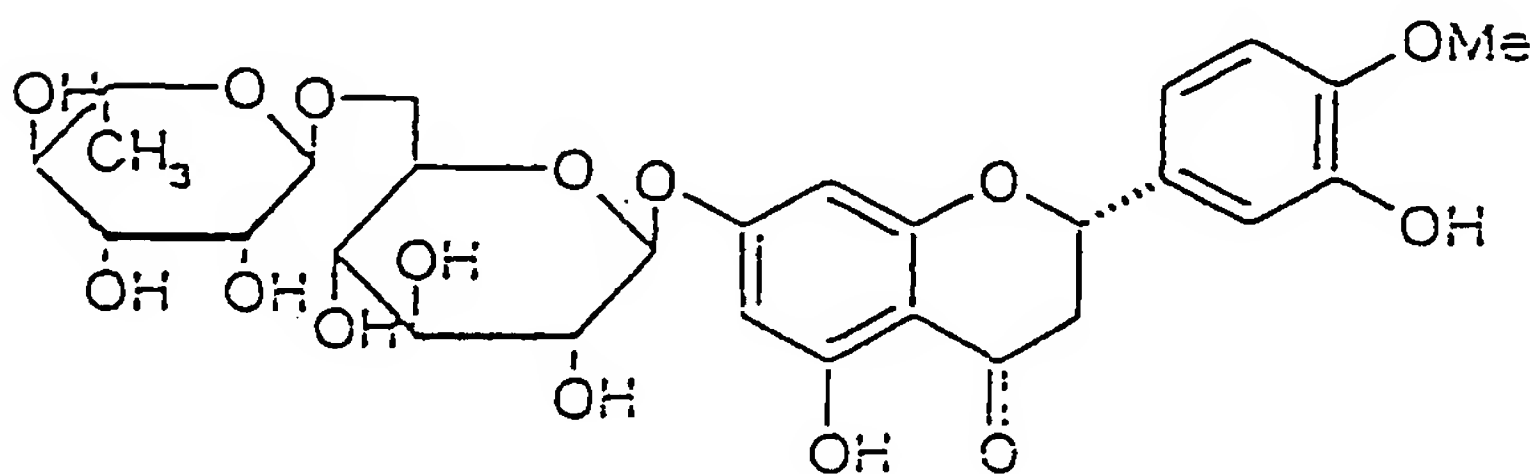
mono and polyalcohols or thiols: 2-thiouracil (QI), 2-mercaptoethanol (QII), esperidine (QIII), secalciferol (QIV), 1- α -OH vitamin D2 (QV), flocalcitriol (QVI), 22-oxacalcitriol (QVII), the vitamin D3 derivative esterified with the vitamin A radical (QVIII), the formula (QIX) compound, 24,28-methylene-1 α -hydroxyvitamin D2 (QX) the compound derived from 1 α ,25-dehydroxyvitamin D2 (QXI), 2-mercaptoimidazol (QXII)



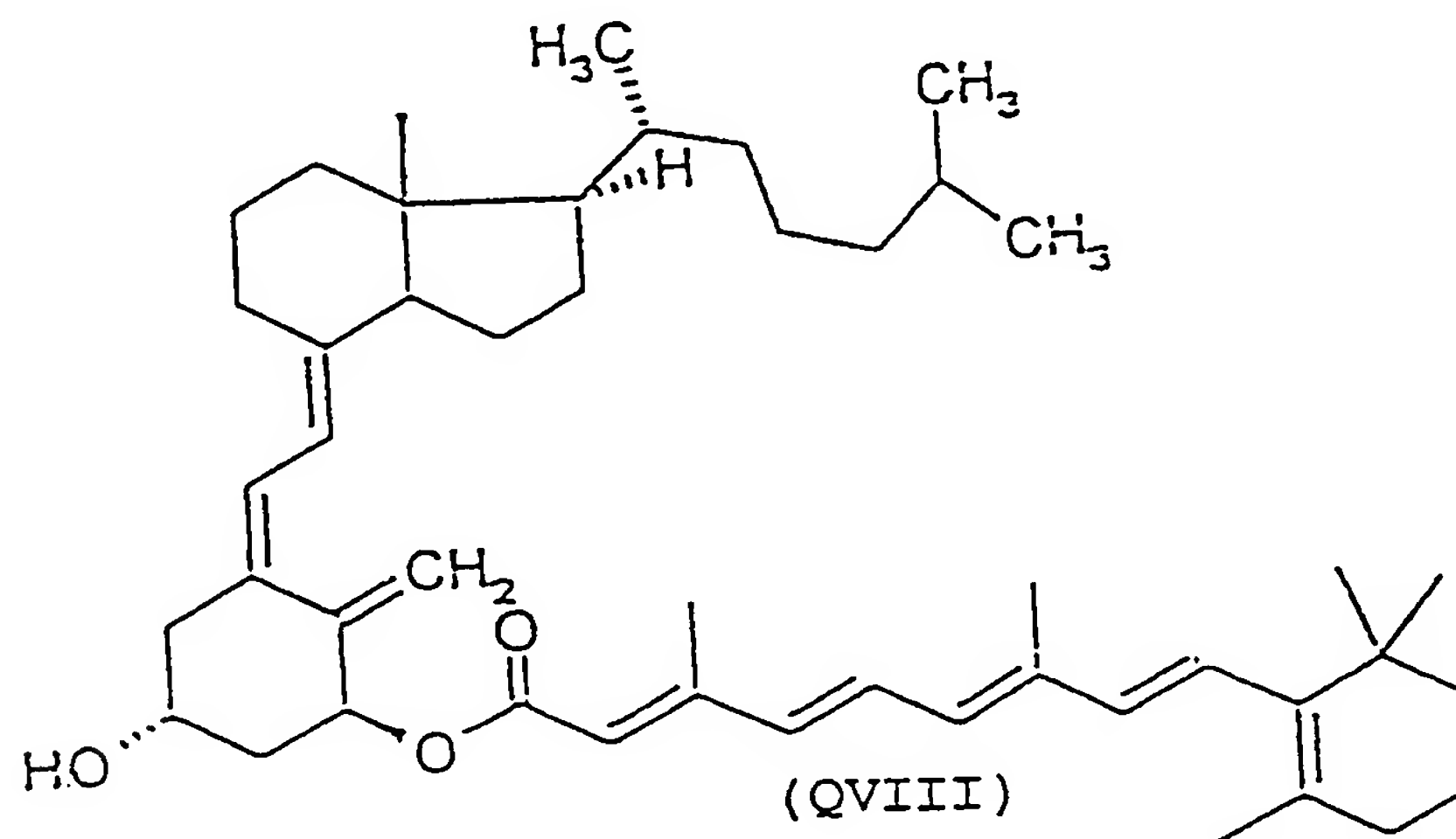
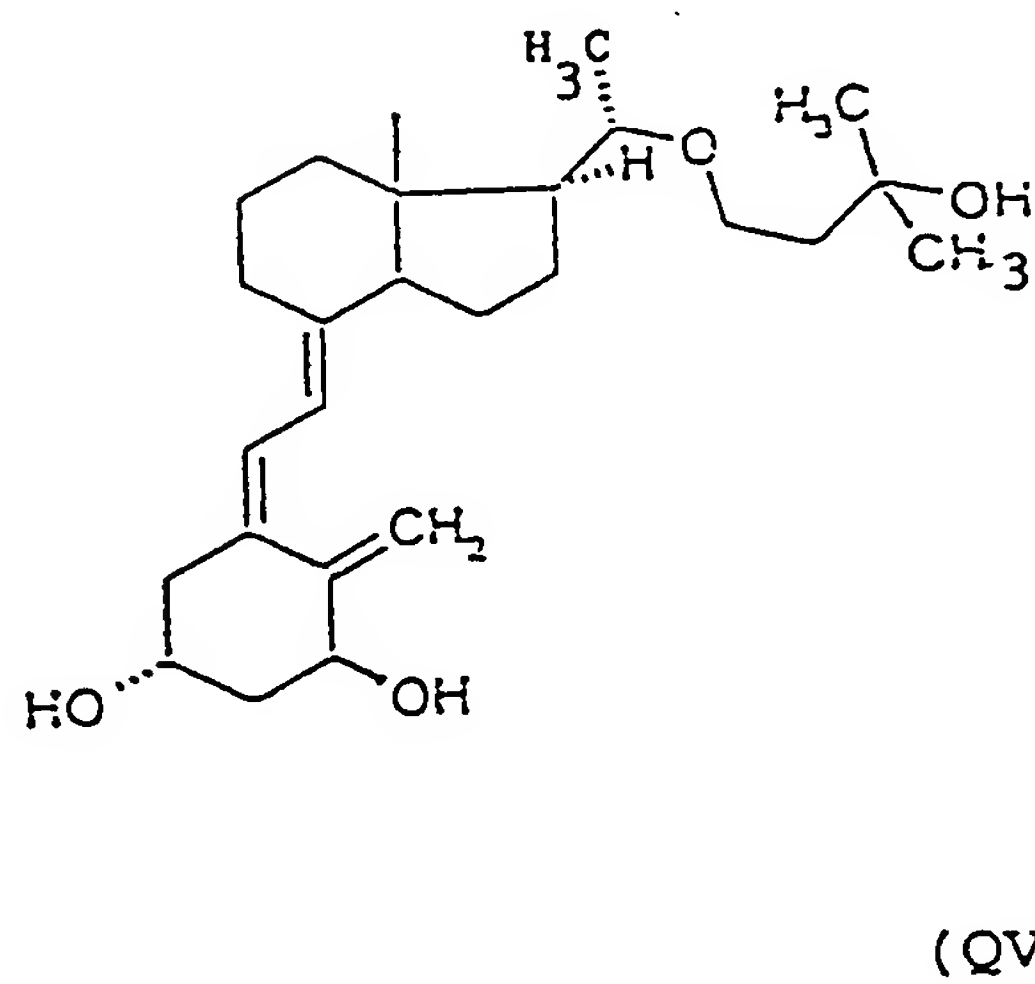
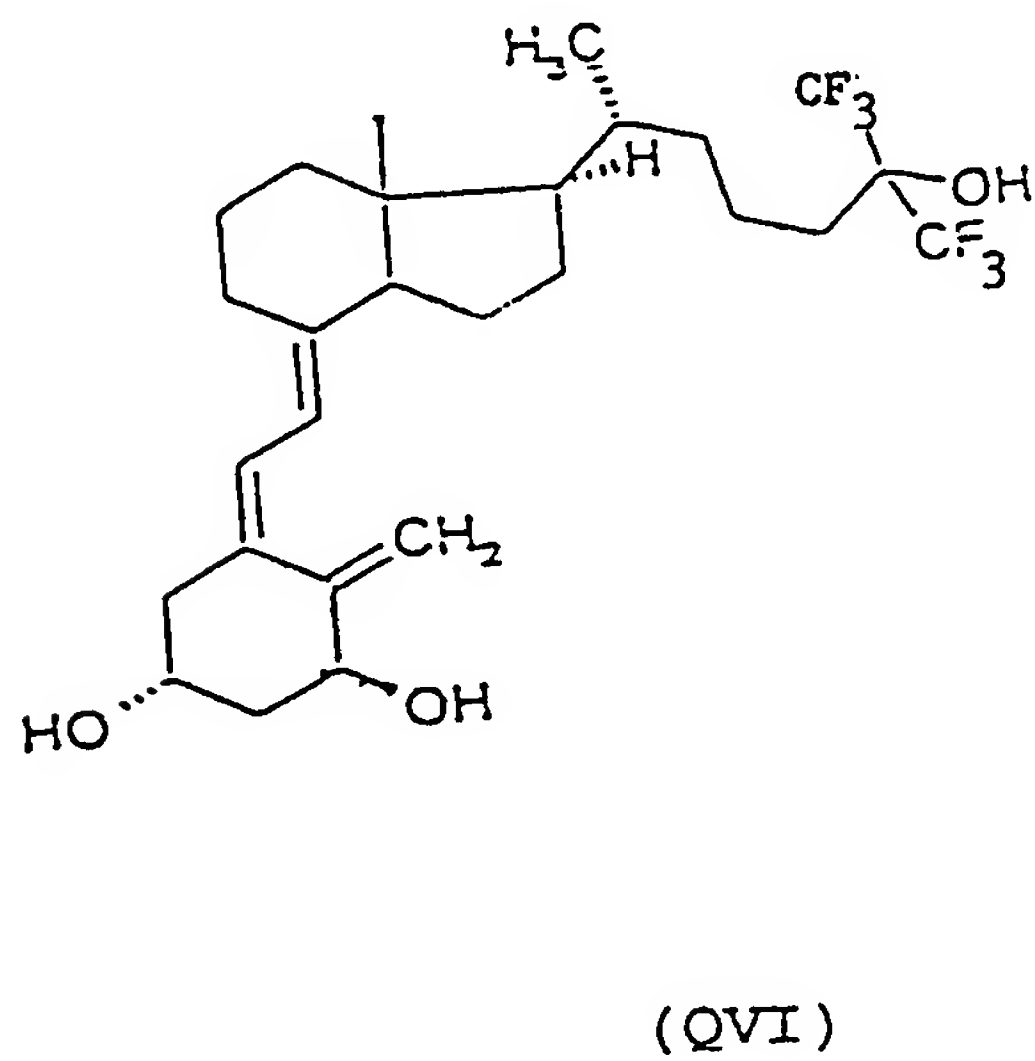
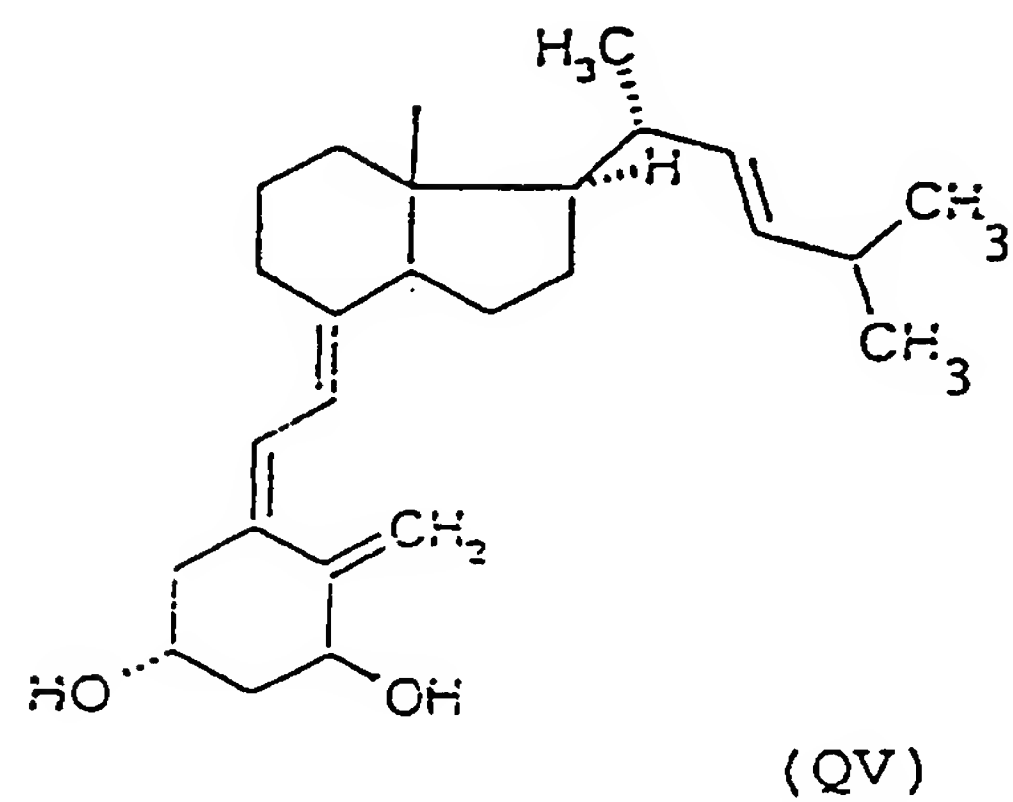
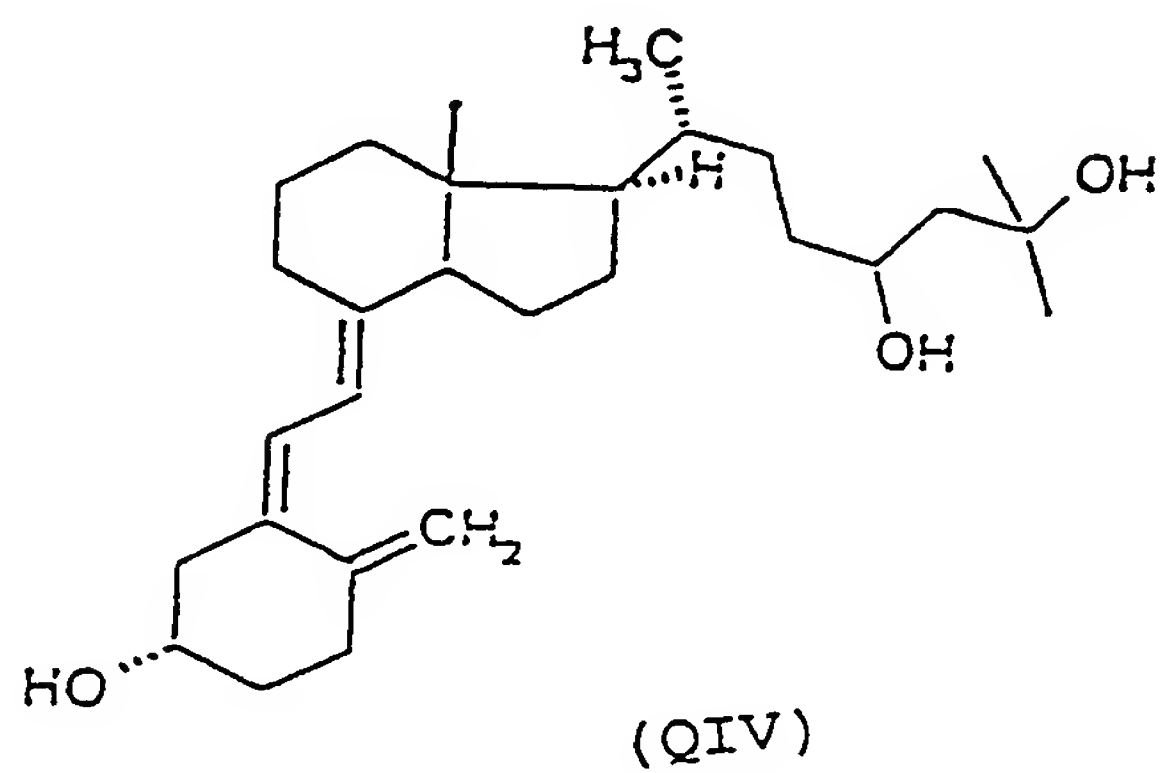
(QI)

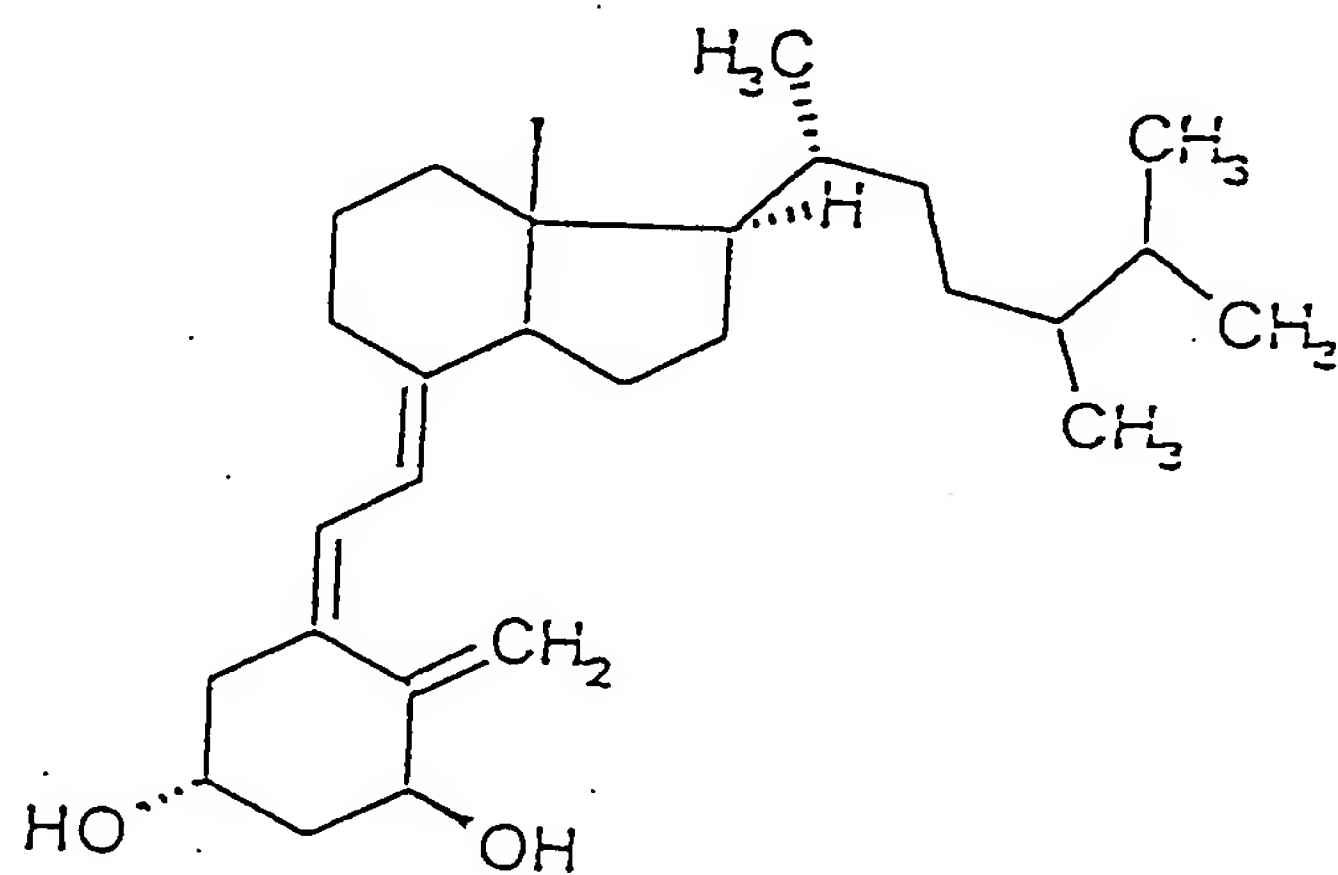


(QII)

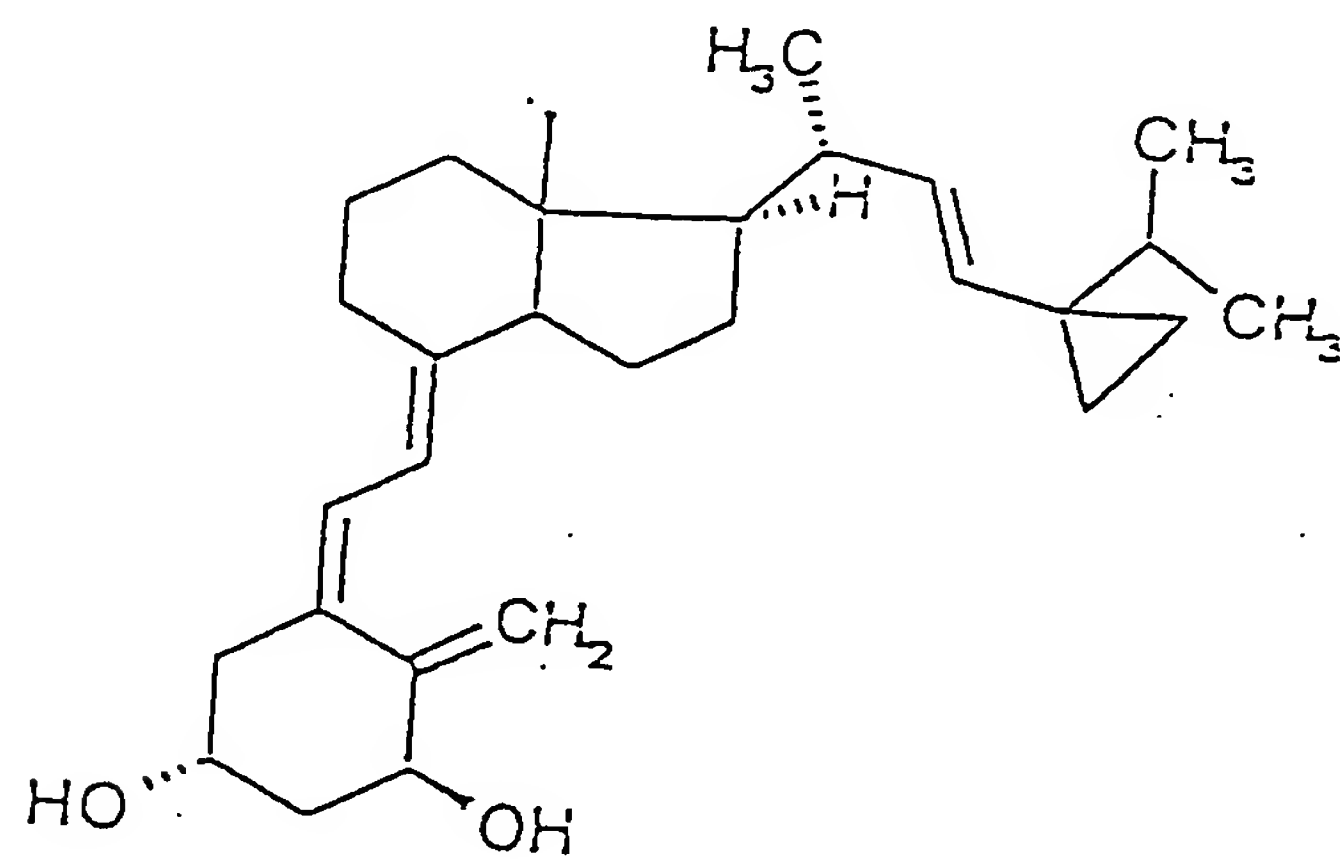


(QIII)

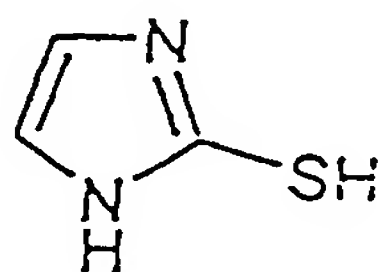




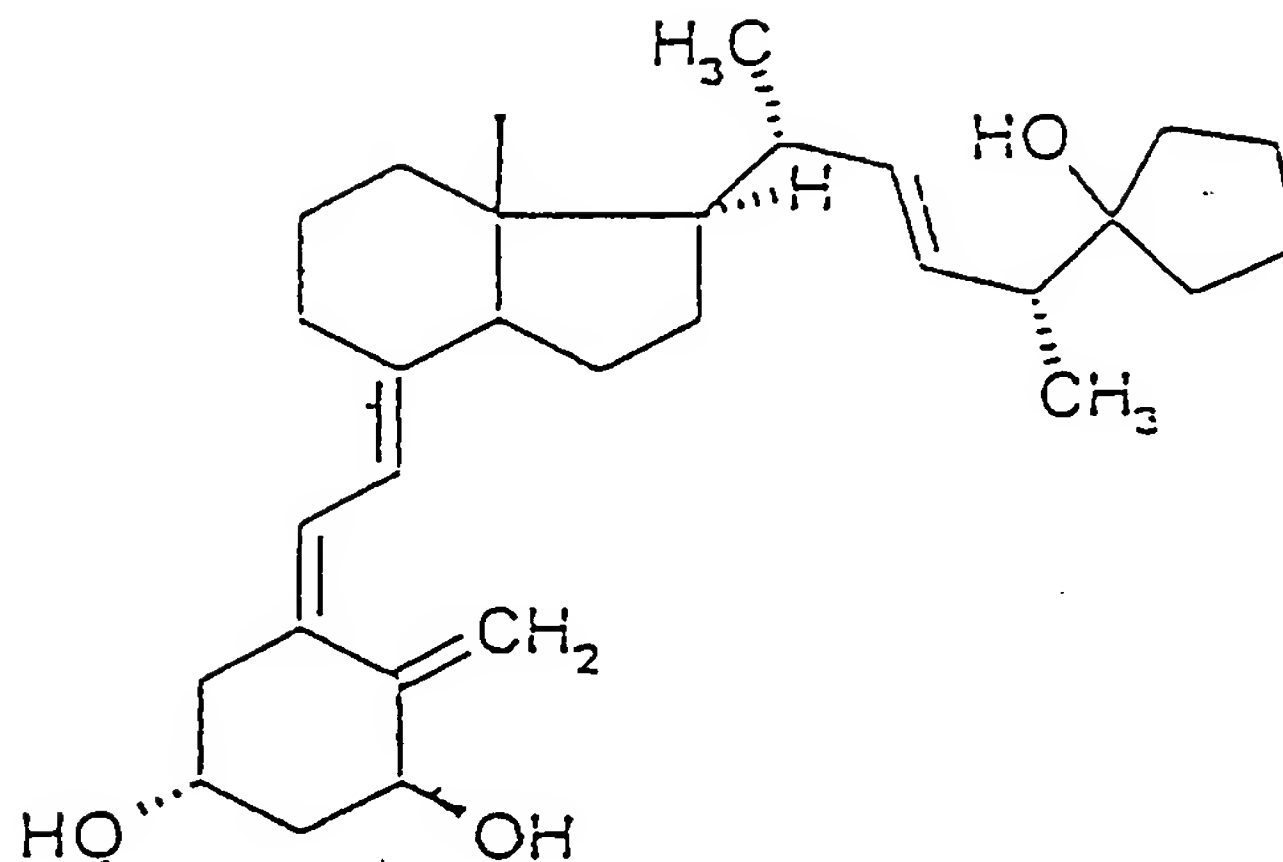
(QIX)



(QX)

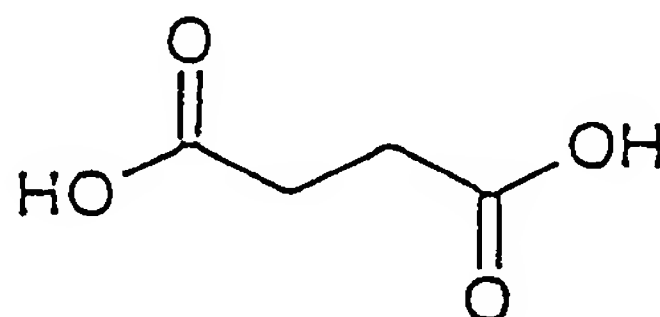


(QXII)



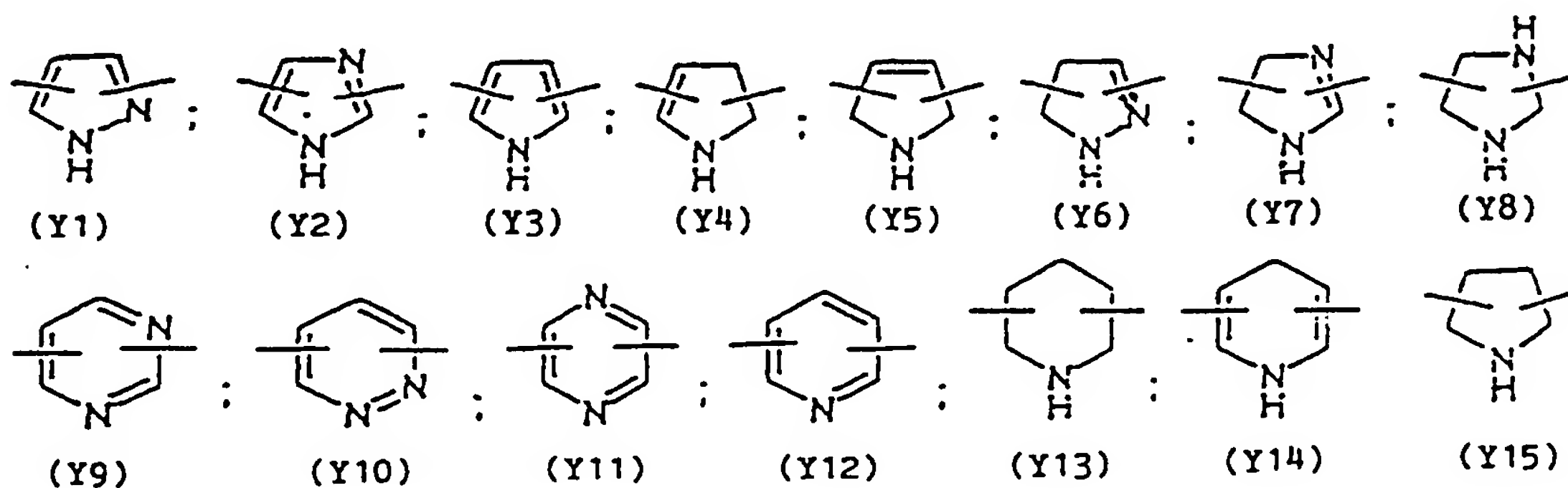
(QXI)

- succinic acid (RI)



(RI)

4. Compounds according to claims 1-2 wherein the precursors of B and B₁ are those meeting test 4.
5. Compounds according to claims 1-4 wherein Y³ in formula (III) is selected from the following:



6. Compounds according to claim 5 wherein Y³ is Y12 (pyridyl)

substituted in positions 2 and 6.

7. Compounds according to claims 1-6 wherein in the precursor steroids $R'' = -CO-CH_2OH$, $-CH(CH_3)-CH_2-CH_2-COOH$.
8. Compounds according to claims 1-7 wherein in the precursor steroids the hydroxyl function is in position 3 and/or in position 11, and/or having in R'' an hydroxyl or carboxylic function in terminal position.
9. Compounds according to claims 1-8; wherein the precursor steroids are selected from the following: Budesonide, Hydrocortisone, Alclomethasone, Algestone, Beclomethasone, Betamethasone, Chloroprednisone, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Cortisone, Corticosterone, Deflazacort, Desonide, Desoximethasone, Dexamethasone, Diflorasone Diflucortolone, Difluprednate, Fluazacort, Flucloronide, Flumethasone, Flunisolide, Fluocinolone Acetonide, Fluocinonide, Fluocortyn Butyl, Fluocortolone, Fluorometholone, Fluperolone Acetate, Fluprednidene Acetate, Fluprednisolone, Flurandrenolide, Formocortal, Halcinonide, Halobetasol Propionate, Halomethasone, Halopredone Acetate, Hydrocortamate, Loteprednol Etabonate, Medrysone, Meprednisone, Methylprednisolone, Momethasone Furoate, Paramethasone, Prednicarbate, Prednisolone, Prednisolone 25-Diethylaminoacetate, Prednisolone Sodium Phosphate, Prednisone, Prednival, Prednylidene, Rimexolone, Triamcinolone, Triamcinolone

Acetonide, 21-Acetoxypregnenolone, Cortivazol, Amcinonide, Fluticasone Propionate, Mazipredone, Tixocortol, Triamcinolone Hexacetonide, Ursodesoxycholic acid, Chenodeoxycholic acid, Mitatrienediol, Moxestrol, Ethynylestradiol, Estradiol, Mestranol.

10. Compounds or salts, or their compositions according to claims 1-9 for use as a medicament; provided that in the compounds of formula (I) are excluded the drugs with $A = R^-$ when $b_0 = 0$ and $C = -T_C-Y_0$ wherein the free valence of Y_0 is saturated as indicated above, and $s = 1$ or 2 .
11. Use of the compounds or salts, or their compositions according to claims 1-9 for the preparation of drugs for the therapeutic stress oxidative use; in the compounds of formula (I) when $b_0 = 0$ and $C = -T_C-Y_0$ wherein the free valence of Y_0 is saturated as indicated above, $s = 1$ or 2 , the drug can be $A = R^-$.
12. Pharmaceutical formulations containing as active principle the compounds or their salts of claims 1-9.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



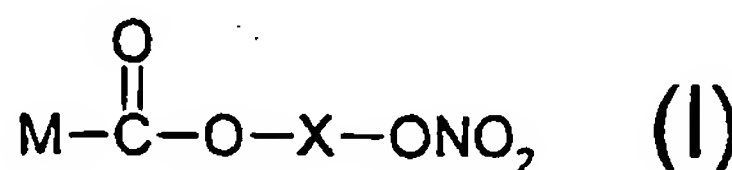
(43) International Publication Date
7 December 2000 (07.12.2000)

PCT

(10) International Publication Number
WO 00/72838 A1

- (51) International Patent Classification⁷: A61K 31/04, 31/196, 31/33, A61P 1/04, 31/00 (74) Agent: ASTRAZENECA AB; Global Intellectual Property, Patents, S-151 85 Södertälje (SE).
- (21) International Application Number: PCT/SE00/01071 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (22) International Filing Date: 25 May 2000 (25.05.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9902027-3 1 June 1999 (01.06.1999) SE
9904704-5 21 December 1999 (21.12.1999) SE
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): EEK, Arne [SE/SE]; AstraZeneca R & D Södertälje, S-151 85 Södertälje (SE). RAUD, Johan [SE/SE]; AstraZeneca R & D Södertälje, S-151 85 Södertälje (SE).
- Published:
— With international search report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW USE OF COMPOUNDS AS ANTIBACTERIAL AGENTS



(57) Abstract: The present invention discloses a new use of NO-releasing NSAIDs, especially NO-releasing NSAIDs of formula (I), or a pharmaceutically acceptable salt or enantiomer thereof, for the manufacture of a medicament for the treatment of bacterial infections, especially caused or mediated by *Helicobacter pylori*. Disclosed is also the new use of a NO-releasing NSAID in combination with an acid susceptible proton pump inhibitor for the treatment of bacterial infections.

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NEW USE OF COMPOUNDS AS ANTIBACTERIAL AGENTS

Field of the invention

5 The present invention is directed to a new use of nitric oxide-releasing Non Steriodal Antiinflammatory Drugs (NO-releasing NSAIDs). More particularly the invention is directed to the use of NO-releasing NSAIDs for the manufacture of a medicament for the treatment of bacterial infections, particularly caused or mediated by *Helicobacter pylori* as well as a combination with acid susceptible proton pump inhibitors for the treatment of
10 bacterial infections.

Background of the invention and prior art

NSAIDs, are among the most commonly prescribed and used drugs world~~wide~~^{WIDE}. Despite the
15 therapeutic benefits of NSAIDs, their use is limited. The use of NSAIDs may lead to gastric mucosal damage due to inhibited production of prostaglandins which increases the risk of gastrointestinal side-effects.

A recent proposal for reducing the side-effects associated with NSAIDs treatment is to use
20 nitric oxide-releasing NSAID derivatives (NO-releasing NSAIDs) (*del Soldato P et al., NO-releasing NSAID:s, A novel class of safer and effective antiinflammatory agents; Inflammopharmacology, 1996; 4; 181-188*). NO-releasing NSAIDs reduce the gastrointestinal side-effects but still have the pharmacological activity characteristic of the frequently used NSAIDs.

25

NO-releasing NSAIDs and pharmaceutically acceptable salts thereof are for instance described in WO 94/04484, WO 94/12463, WO 95/09831 and WO 95/30641.

Helicobacter pylori is a gram-negative spirilliform bacteria which colonises in the gastric
30 mucosa. The relationship between gastrointestinal disorders and infections with

Helicobacter pylori proposed in 1983 by Warren (*Warren JR Lancet 1983;1.1273*) is well established today.

A number of different therapies have been proposed for the treatment of *Helicobacter pylori* infections. Combination therapies are commonly used. The most commonly used comprise a proton pump inhibitor in combination with one or more antibacterial compounds such as claritromycin and amoxicillin. For instance WO93/00327 discloses the combination of a substance with inhibiting effect on the gastric acid secretion which increases the intragastric pH, and an acid degradable antibacterial compound. Some of these therapies also comprise a bismuth compound, se for instance WO 98/03219 and WO98/22117, which latter application discloses a composition containing bismuth, an antimicrobial agent and a non-steriodal antiinflammatory agent for the treatment of gastrointestinal disorders caused or mediated by *Helicobacter pylori*.

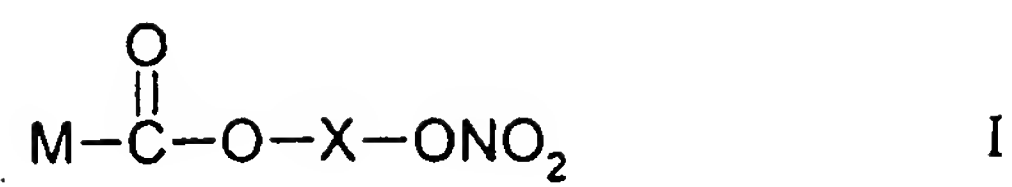
In view of the vast number of the population suffering from gastrointestinal disorders caused or mediated by bacterial infections, such as *Helicobacter pylori* infections, and also in view of the fact that many bacterial strains develop a resistance to commonly used antibiotics, a continuing need exists for a safe and effective medicament having an antibacterial effect, especially for the treatment of *Helicobacter pylori* infections.

Outline of the invention

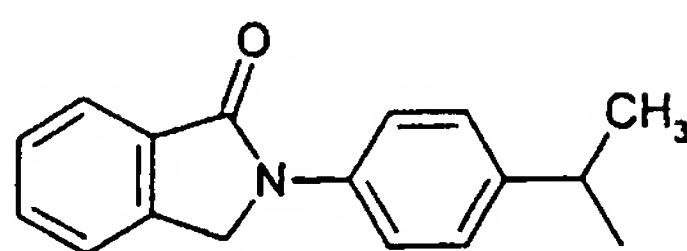
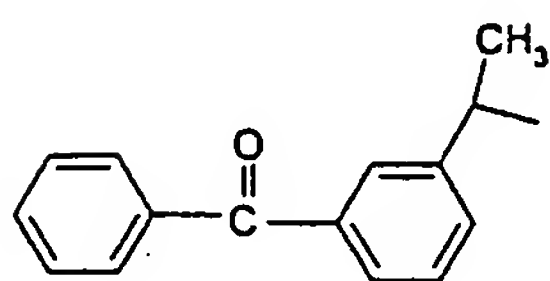
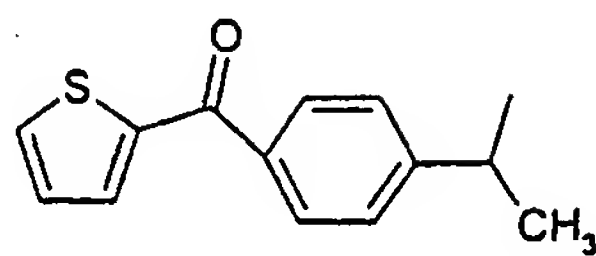
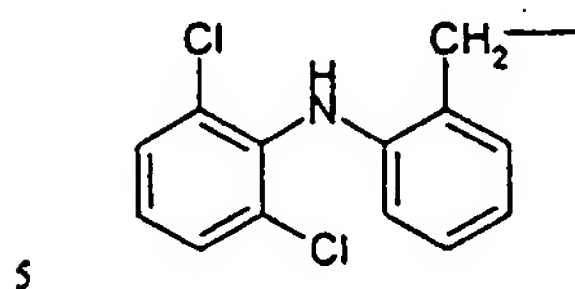
It has now surprisingly been found that NO-releasing NSAIDs have an antibacterial effect, which makes them useful for the treatment of bacterial infections.

The present invention is related to the use of a NO-releasing NSAID as well as pharmaceutically acceptable salts or enantiomers thereof, for the manufacture of a medicament for the treatment of bacterial infections.

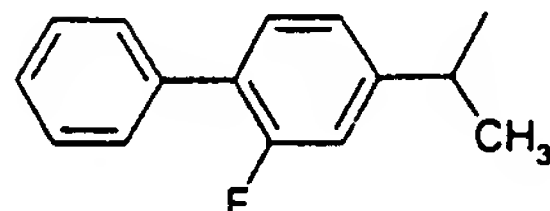
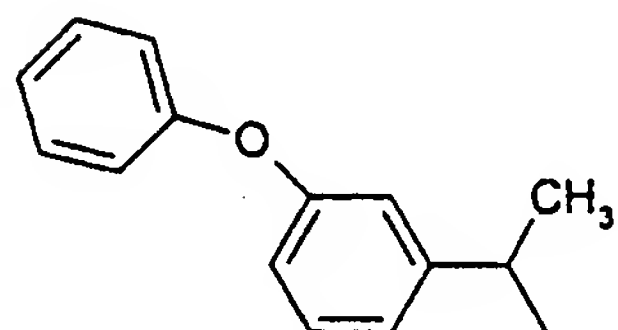
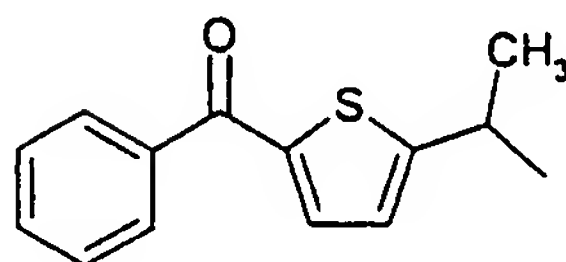
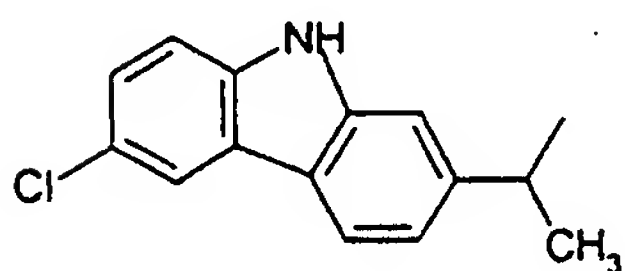
Preferably the NO-releasing NSAID is defined by the formula I



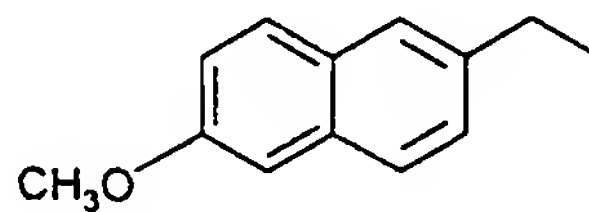
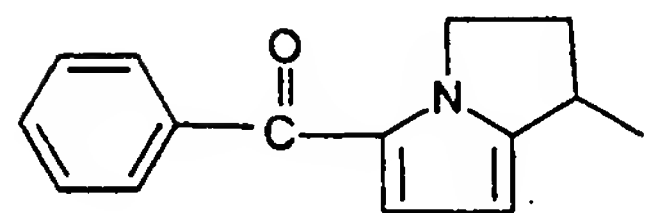
wherein M is selected from any one of

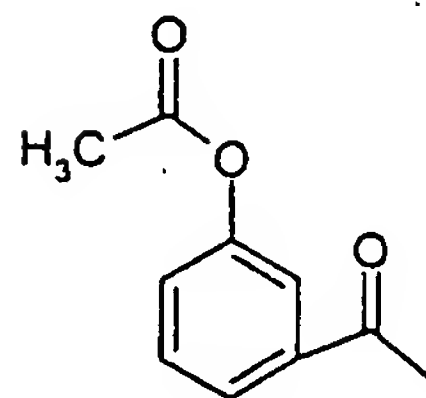
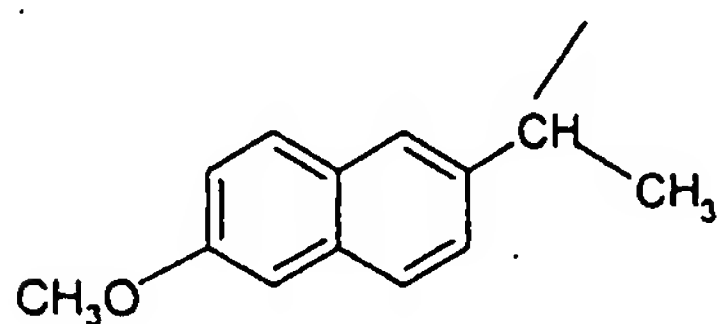
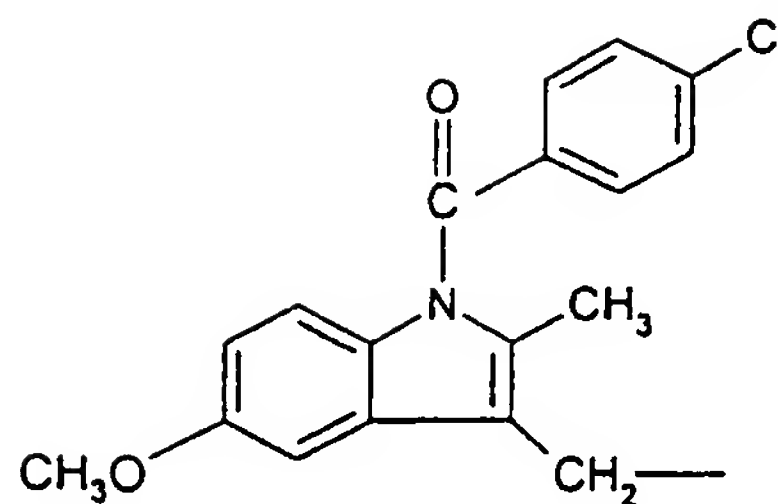
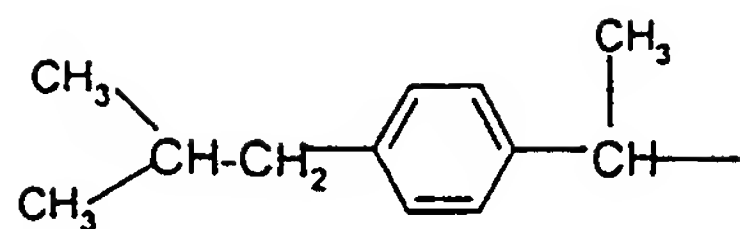


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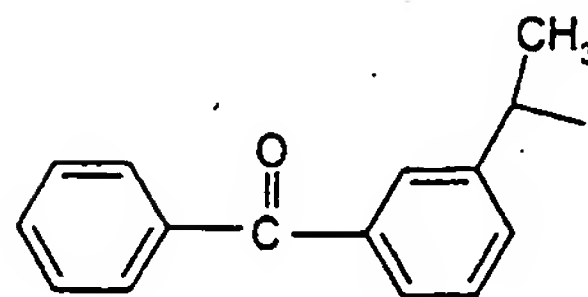
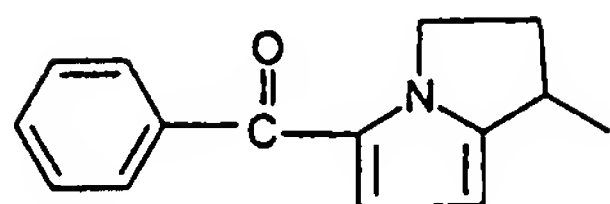
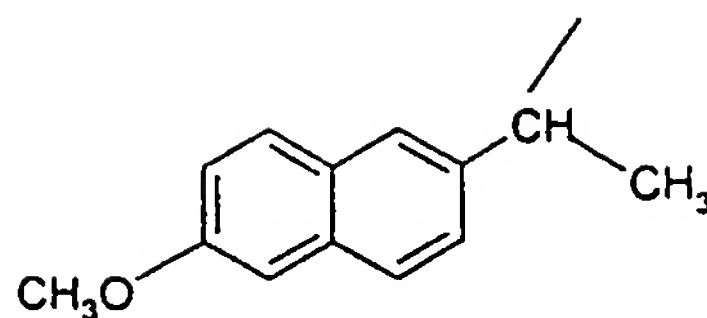
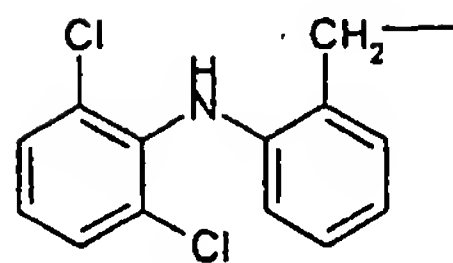
5

and X is a spacer, i.e. a compound forming a bridge between the nitrogen oxide donating group and the NSAID moiety, or a pharmaceutically acceptable salt or enantiomer thereof;

- 10 X is preferably selected from linear, branched or cyclic $-(\text{CH}_2)_n-$ wherein n is an integer of from 2 to 10; $-(\text{CH}_2)_m-\text{O}-(\text{CH}_2)_p-$ wherein m and p are integers of from 2 to 10; and $-\text{CH}_2-p\text{C}_6\text{H}_4-\text{CH}_2-$.

M is not limited by the above definition but may be any other compound giving the
15 corresponding NSAID by hydrolysis of the compound according to formula I.

In a preferred embodiment of the invention M is selected from



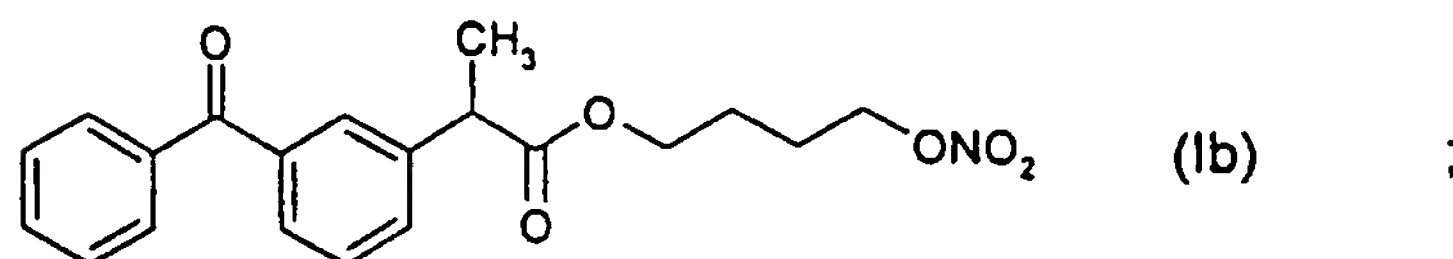
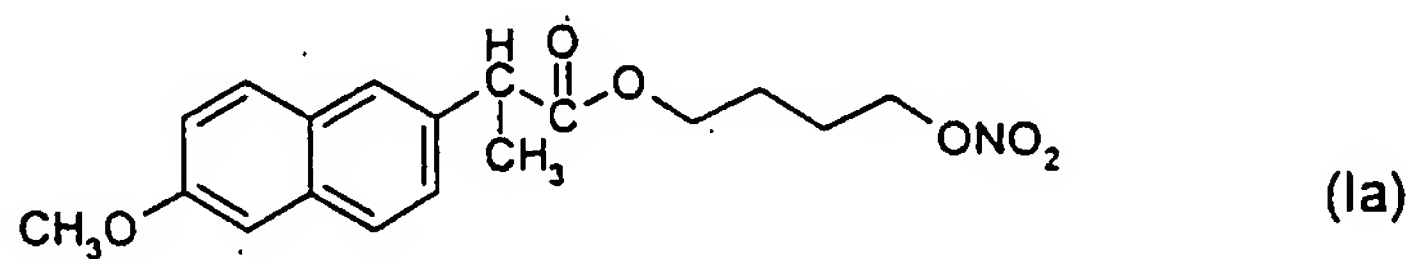
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and X is selected from

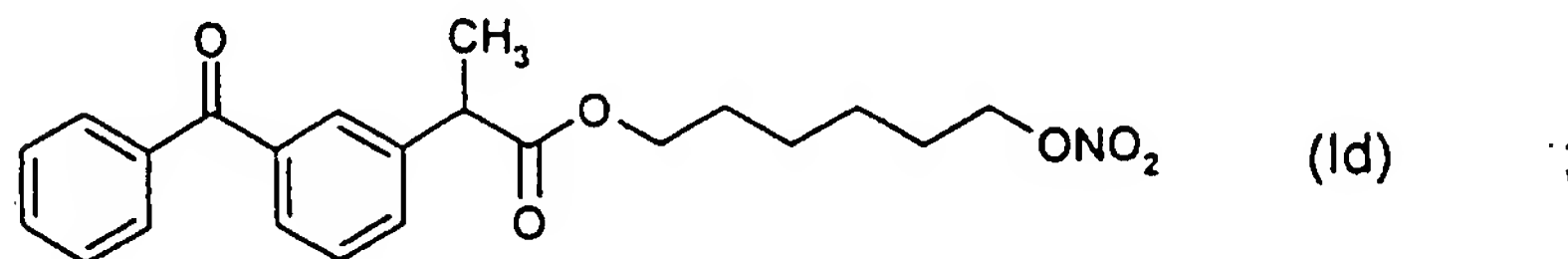
linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6;

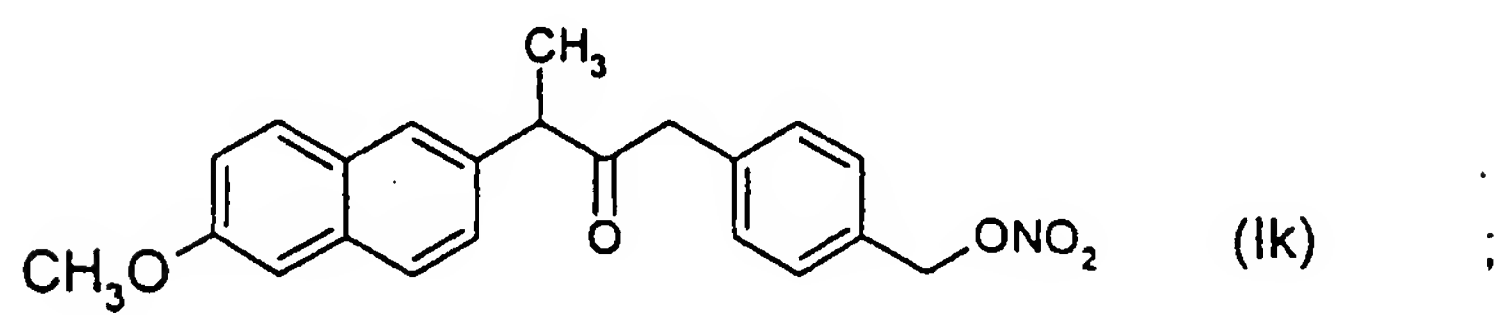
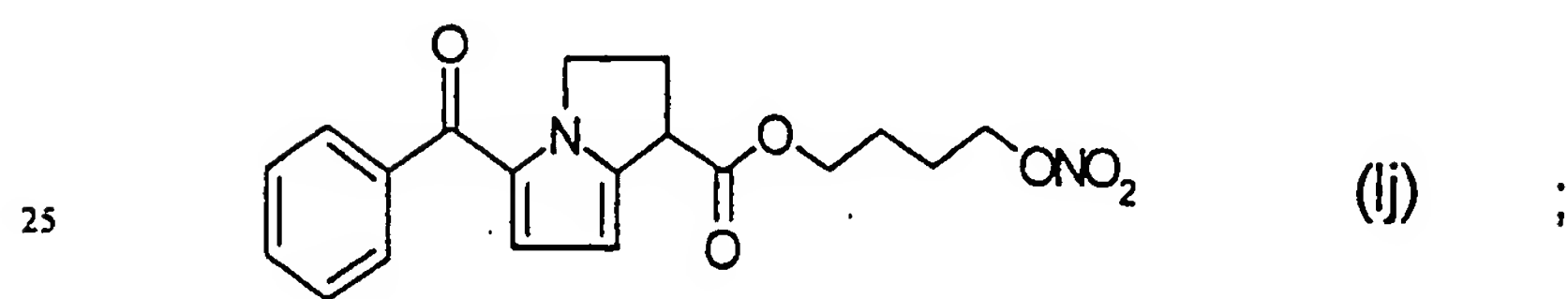
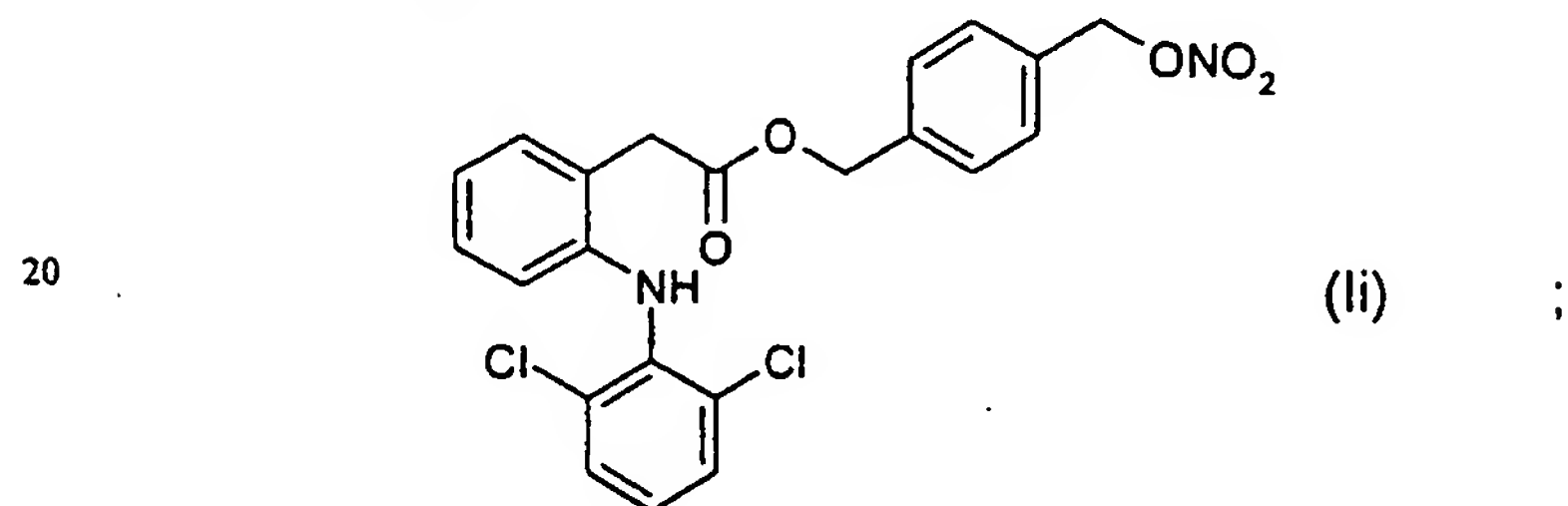
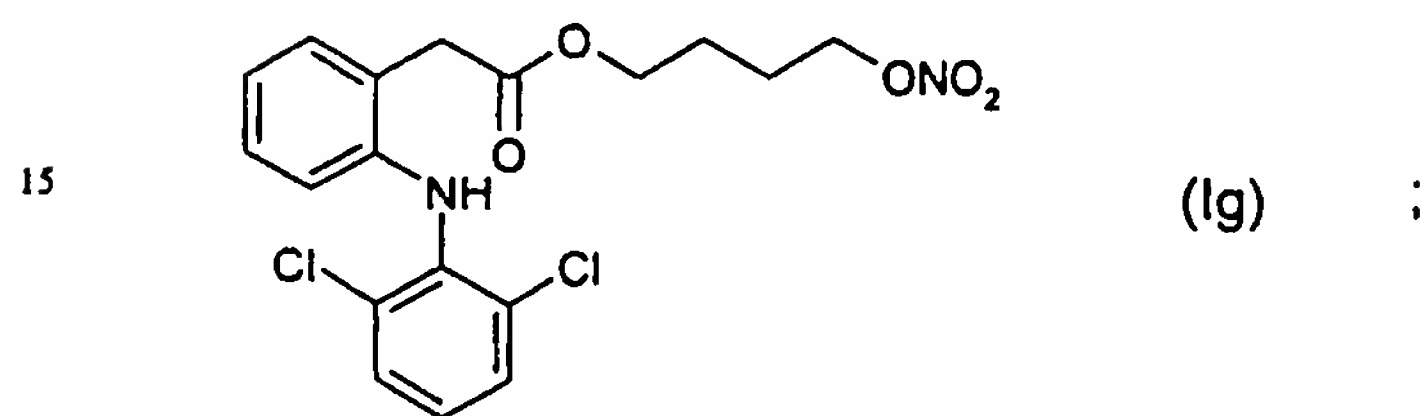
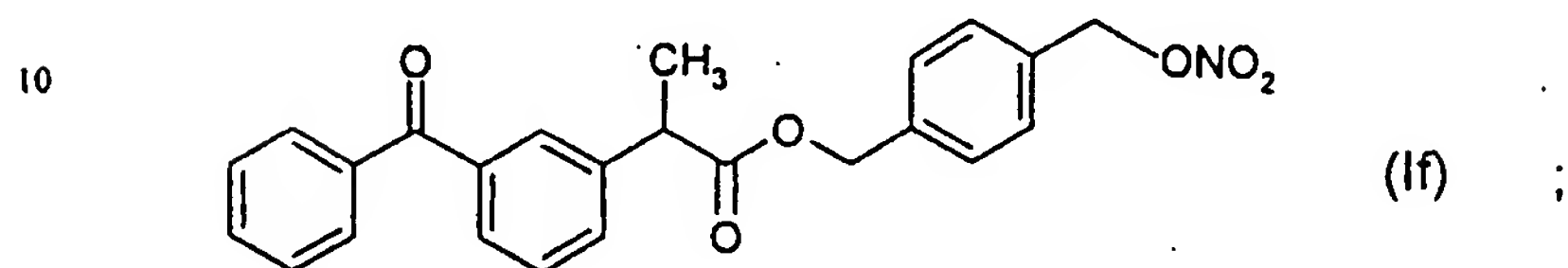
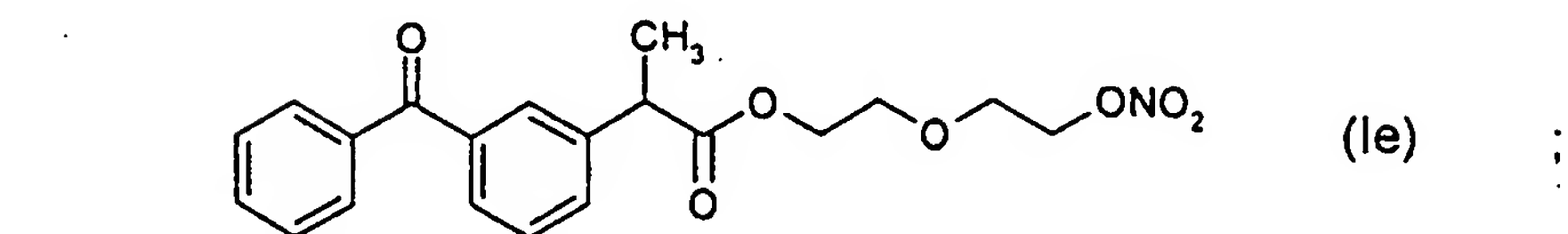
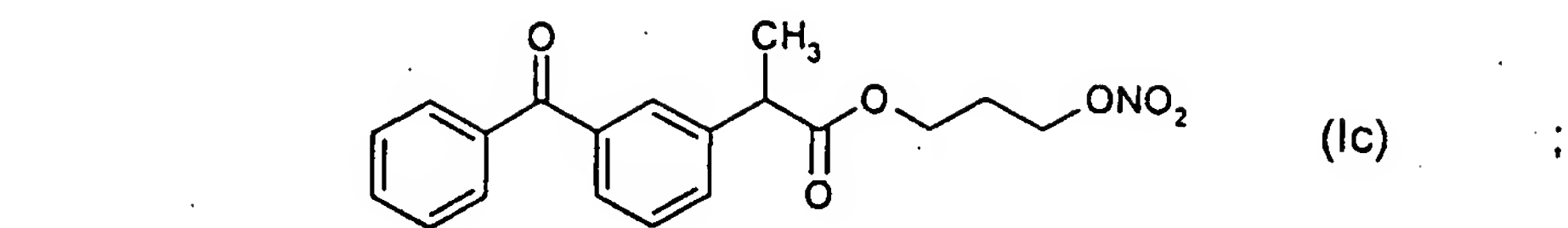
$-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

- 10 In an even more preferred embodiment of the invention the NO-releasing NSAID is a compound according to any one of the formulas

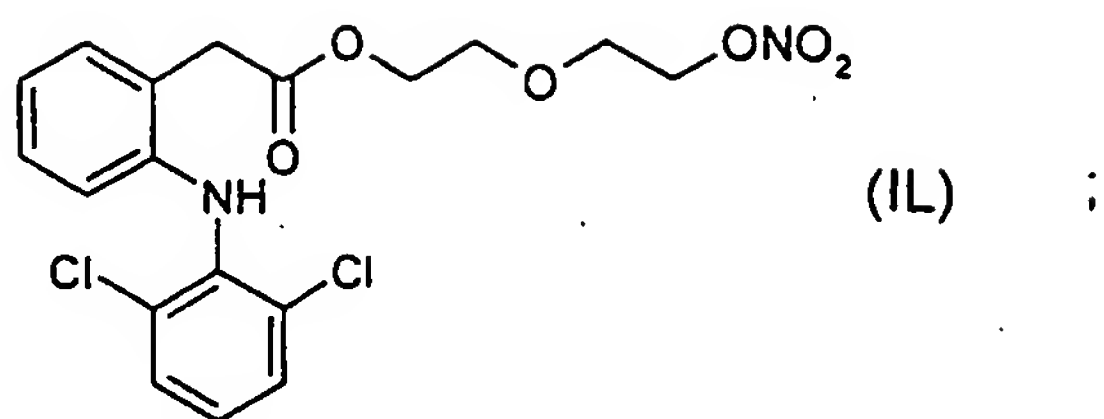


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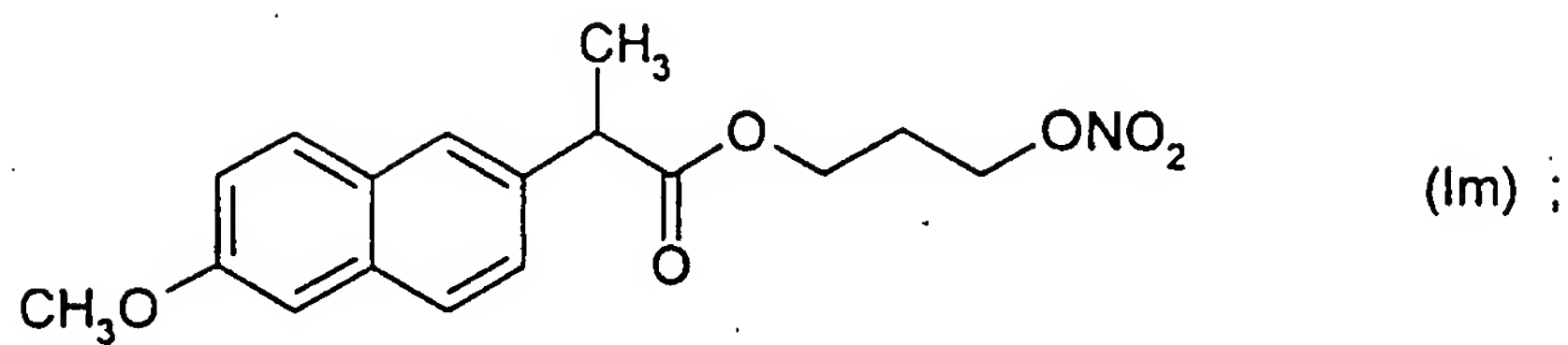




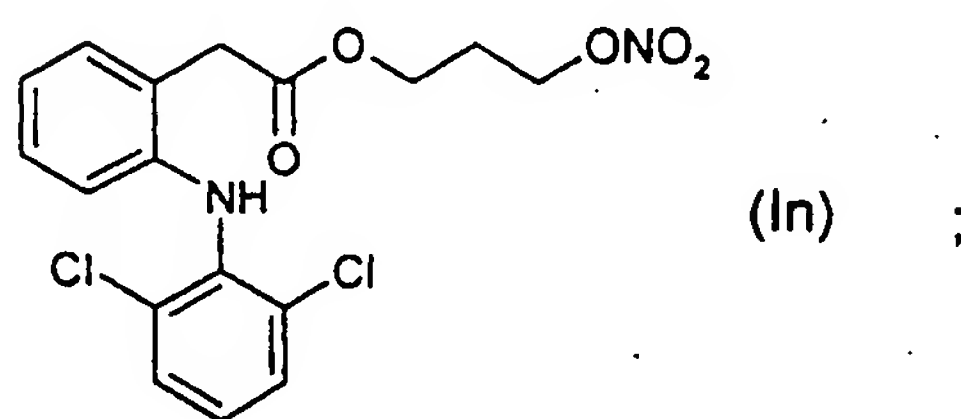
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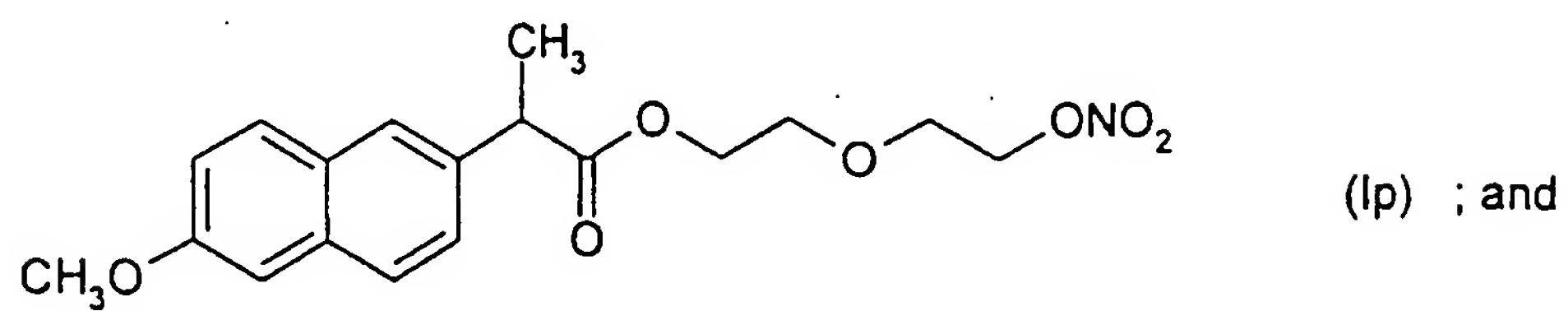
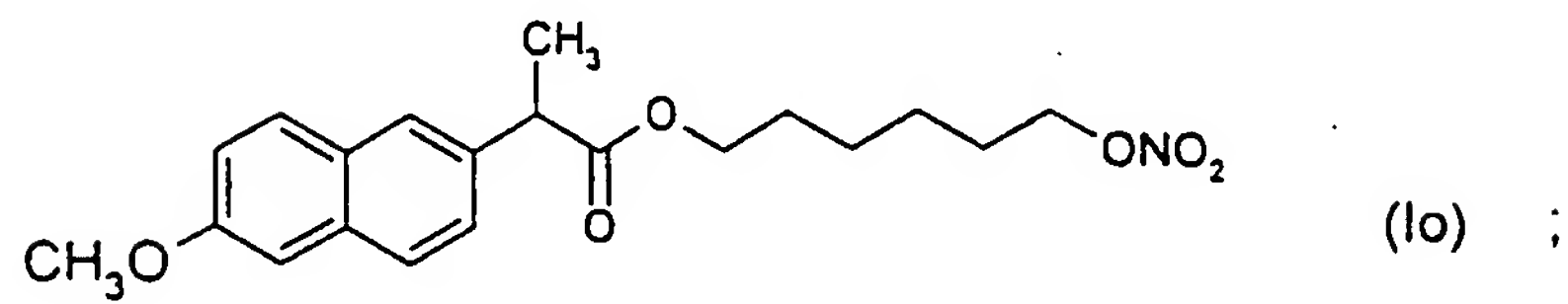
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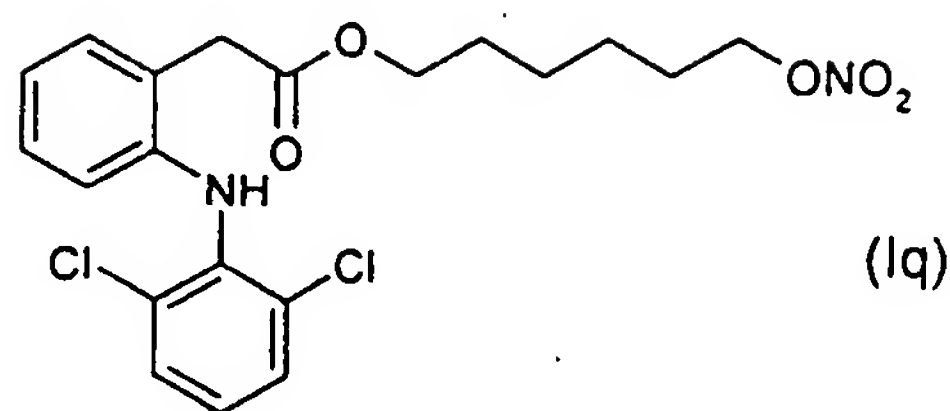


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In a particularly preferred embodiment of the invention the NO-releasing NSAID is a compound according to formula Ia.

A further aspect of the invention is the use of a NO-releasing NSAID, preferably a compound of the formula I above, in the manufacture of a medicament for use in the treatment of *Helicobacter pylori* infections, especially in the treatment of gastrointestinal disorders caused or mediated by *Helicobacter pylori*.

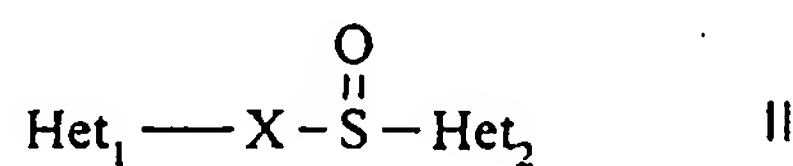
Still a further aspect of the invention is a method for the treatment of bacterial infections, in particular *Helicobacter pylori* infections, whereby an effective amount of a medicament comprising a NO-releasing NSAID, preferably a compound of the formula I, as active agent is administered to a subject suffering from said bacterial infection.

Also a pharmaceutical formulation suitable for use in the treatment of bacterial infections, which formulation comprising a NO-releasing NSAID, preferably a compound of the formula I, is within the scope of the invention.

Furthermore, the invention is related to the use of a NO-releasing NSAID, preferably a compound of the formula I, in combination with an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer in the manufacture of pharmaceutical formulations intended for simultaneous, separate or sequential administration in the treatment of bacterial infections, especially *Helicobacter pylori* infections.

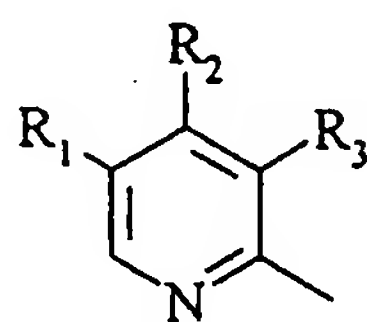
The invention may be applied in combination with other agents generally associated with treatment of bacterial infections, such as for instance antibacterial agents.

An acid susceptible proton pump inhibitor is, for instance, a compound of the general
 5 formula II

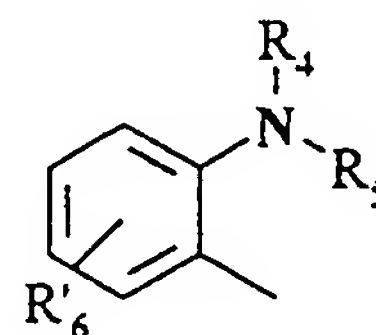


wherein

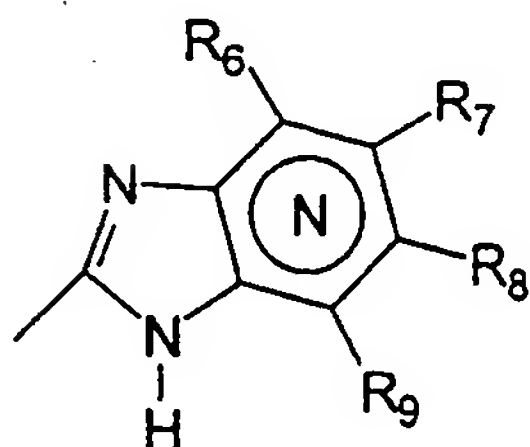
10 Het_1 is



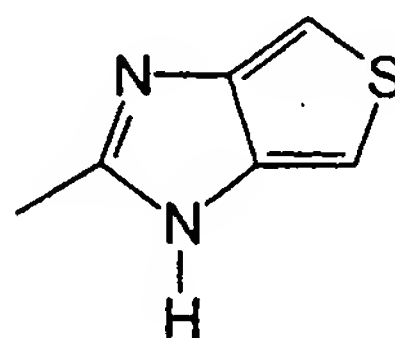
or



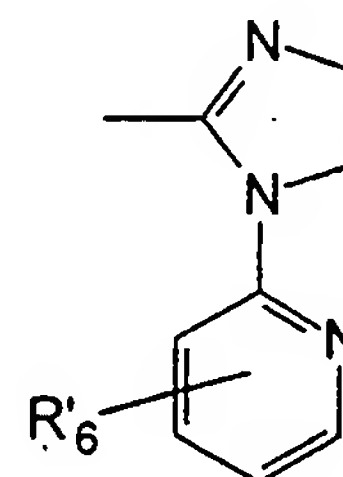
Het_2 is



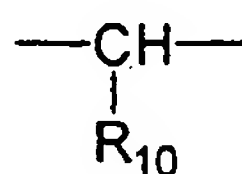
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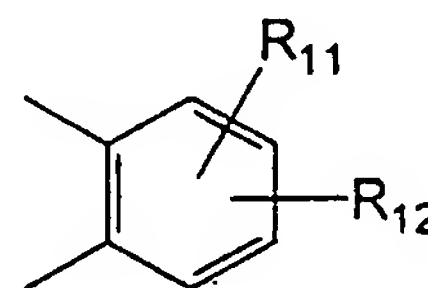
or



15 $\text{X} =$



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6 - R_9
 20 optionally may be exchanged for a nitrogen atom without any substituents;

R_1 , R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

5 R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

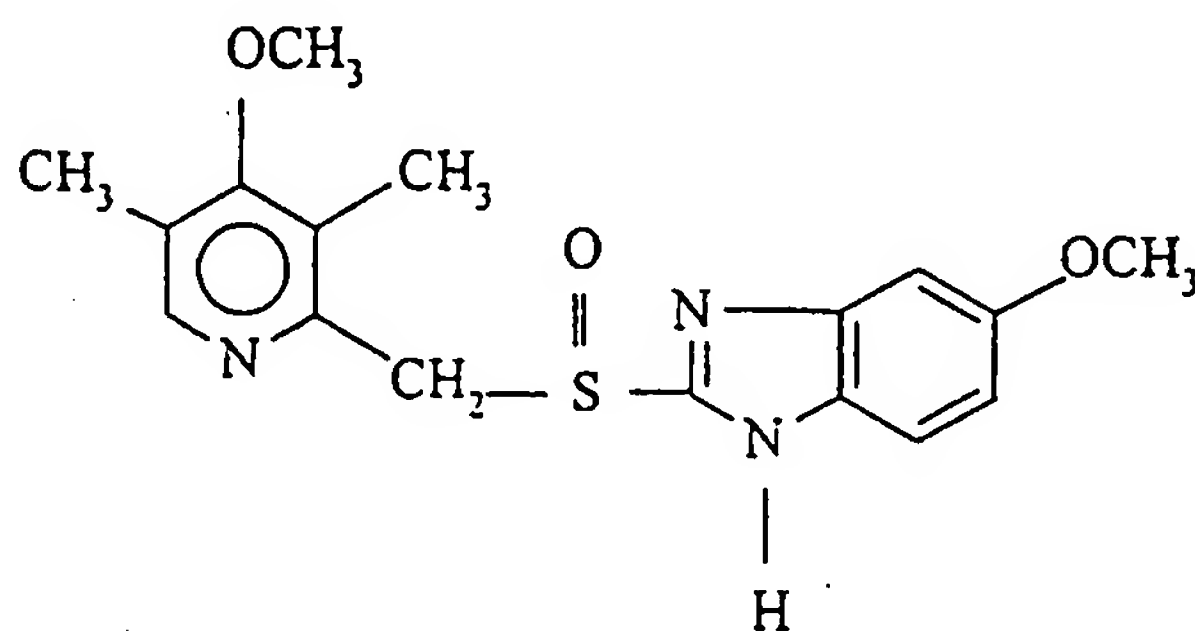
R_6 - R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-
10 alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6 - R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

15 R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof. The substituents may be branched or straight C_1 - C_9 -chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

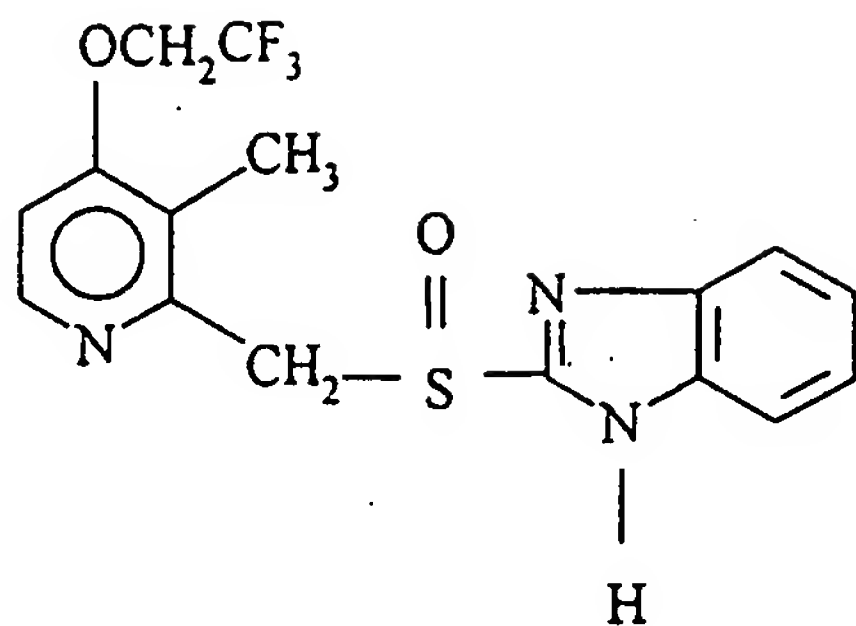
Examples of proton pump inhibitors according to formula II are

20



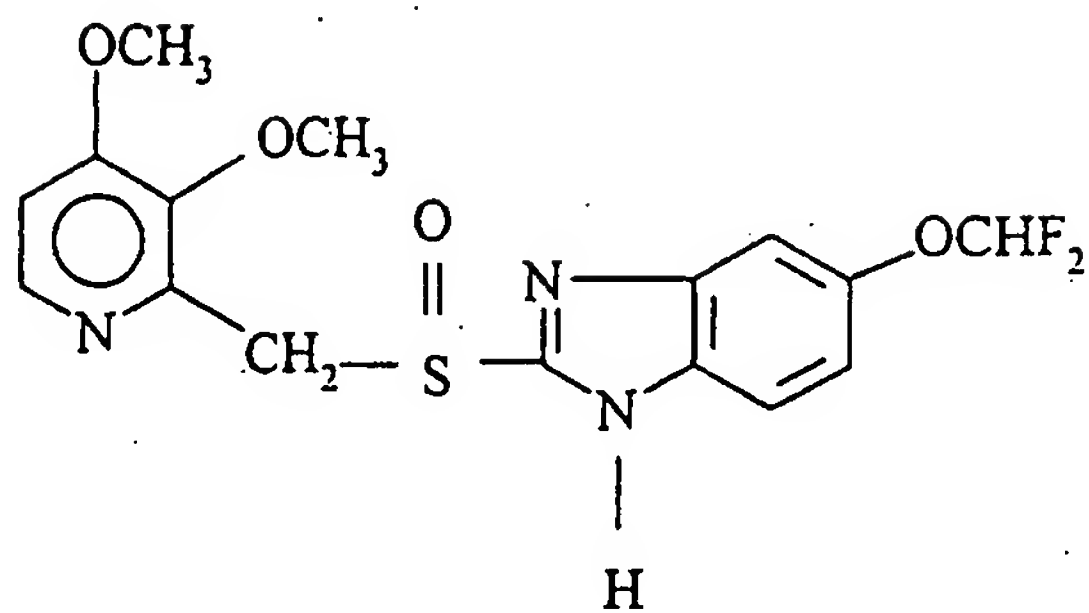
Omeprazole

25

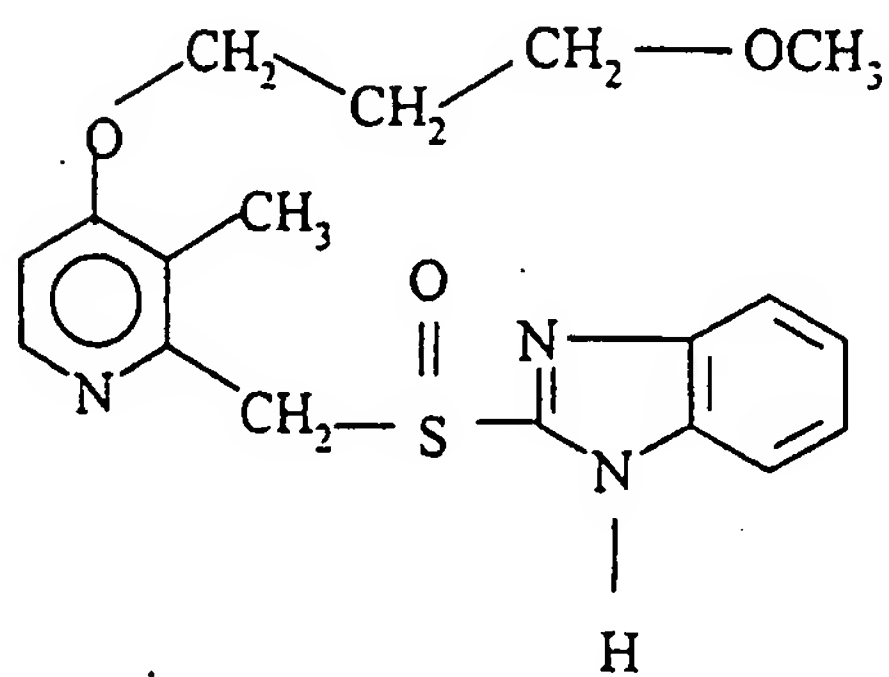


Lansoprazole

5

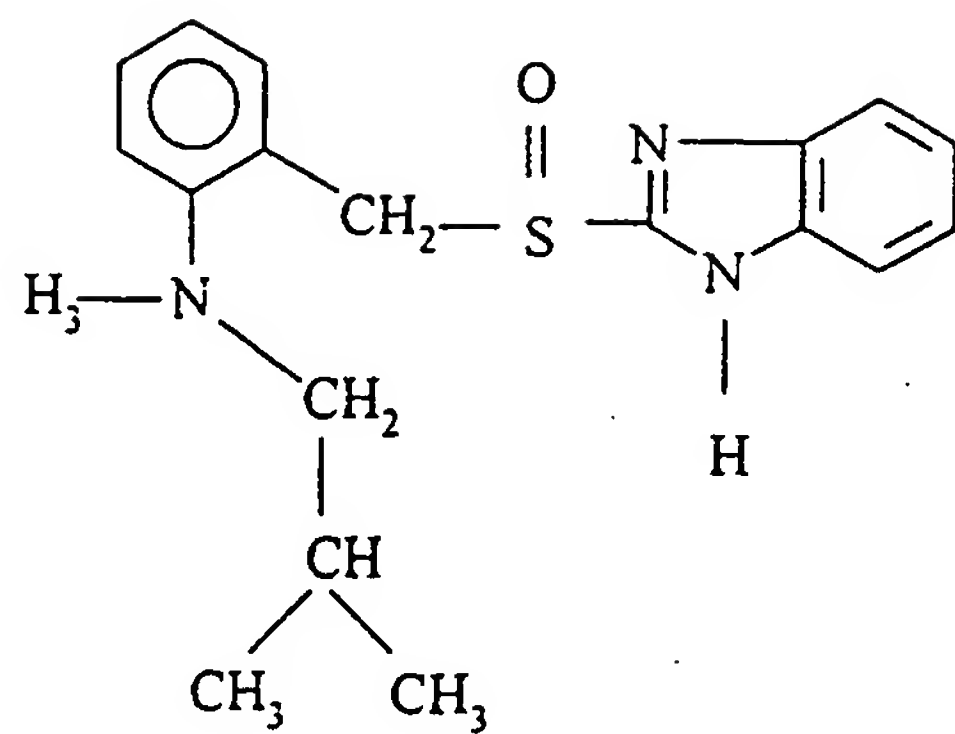


Pantoprazole

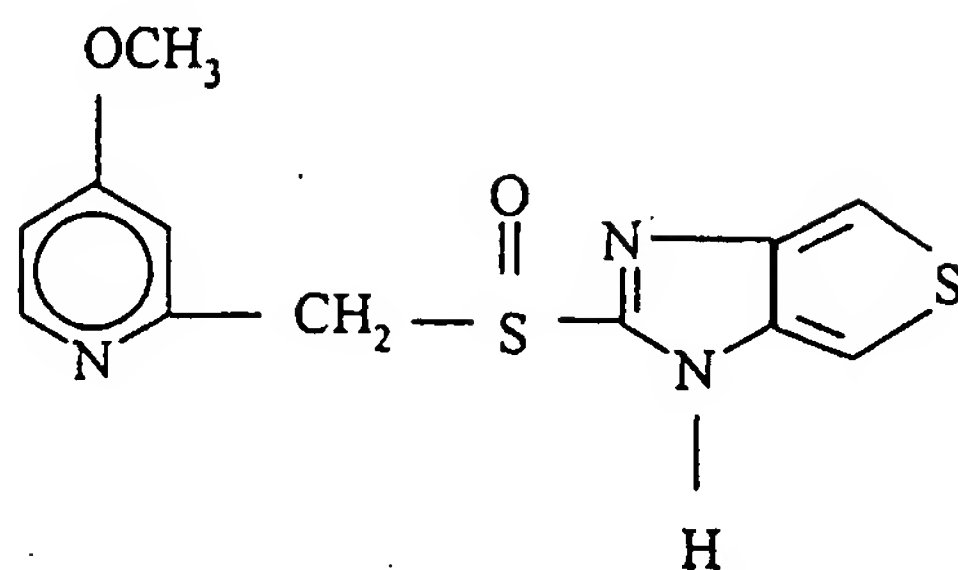


Pariprazole

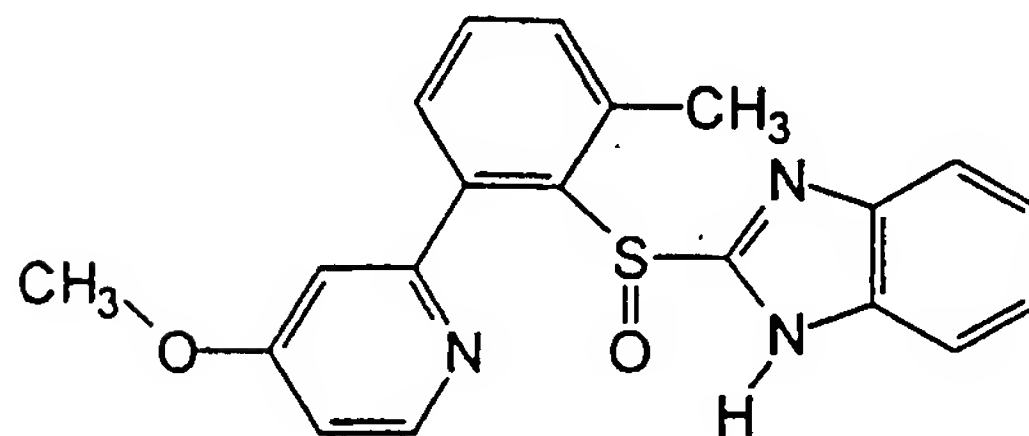
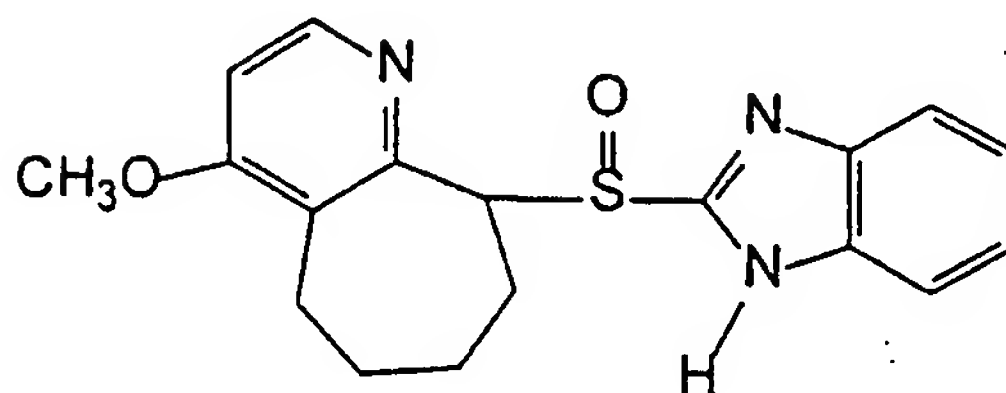
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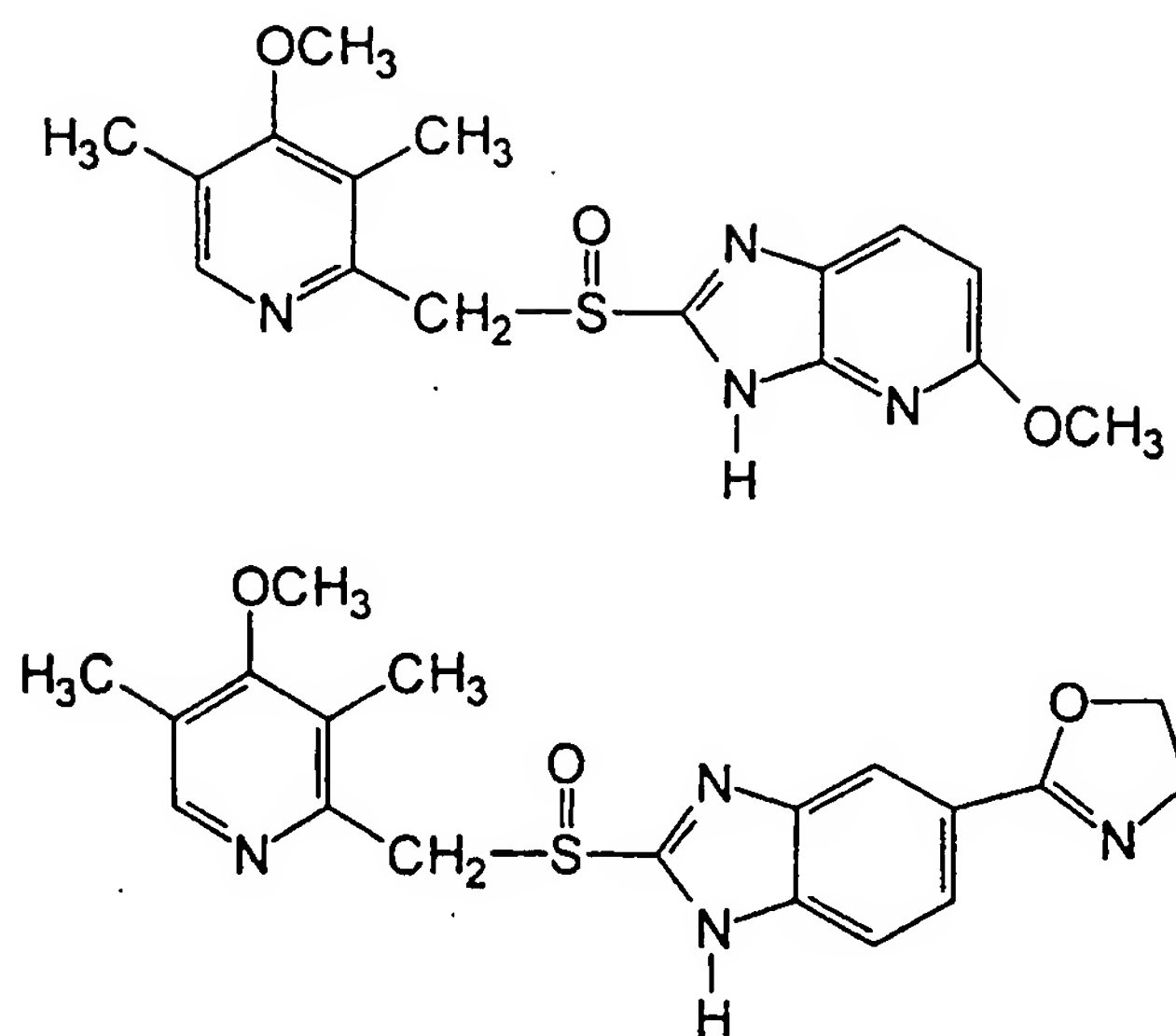


Leminoprazole



5





5 The proton pump inhibitor may also be used in the form of a pharmaceutical acceptable salt or a single enantiomer in the claimed combination.

Preferably the proton pump inhibitor omeprazole, or an alkaline salt of omeprazole, such as the magnesium salt, or (*S*)-omeprazole or an alkaline salt of (*S*)-omeprazole, such as the
10 magnesium salt is used in the claimed combination.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, and further the especially suitable compounds are
15 described in WO95/01977 and WO94/27988.

According to the invention there is further provided a method for treating bacterial infections, particularly *Helicobacter Pylori* infections, which method comprises simultaneous, separate or sequential administration to a subject suffering from a bacterial
20 infection one or more pharmaceutical formulations comprising a NO-releasing NSAID, preferably a compound according to the formula I, and an acid susceptible proton pump

inhibitor. Also pharmaceutical formulations for simultaneous, separate or sequential administration to be used in the treatment of bacterial infections, which formulations comprise an NO-releasing NSAID, preferably a compound of the formula I and an acid susceptible proton pump inhibitor are within the scope of the invention.

5

The NO-releasing NSAID alone or in combination with an acid susceptible compound may be in a dosage form administered orally, rectally, epidurally, intravenously, intramuscularly, subcutaneously, by infusion, nasally or any other way suitable for administration. Preferably the active compound(-s) is administered orally.

10

The active compound(-s) are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active compound(-s) varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0.5 – 5000 mg, preferably 5 – 1000 mg, of the NO-releasing NSAID. If a combination with a proton pump inhibitor is used 0.5 – 5000 mg of the NO-releasing NSAID, and 0.1 – 200 mg of the proton pump inhibitor will be comprised in each dosage form, or in two separate dosage forms. Preferably, the amount of the NO-releasing NSAID in each dosage form is 5 – 1000 mg, and the amount of the proton pump inhibitor 10 - 80 mg.

20

Detailed description of the invention

The invention is described in more detail by the following non-limiting examples.

25

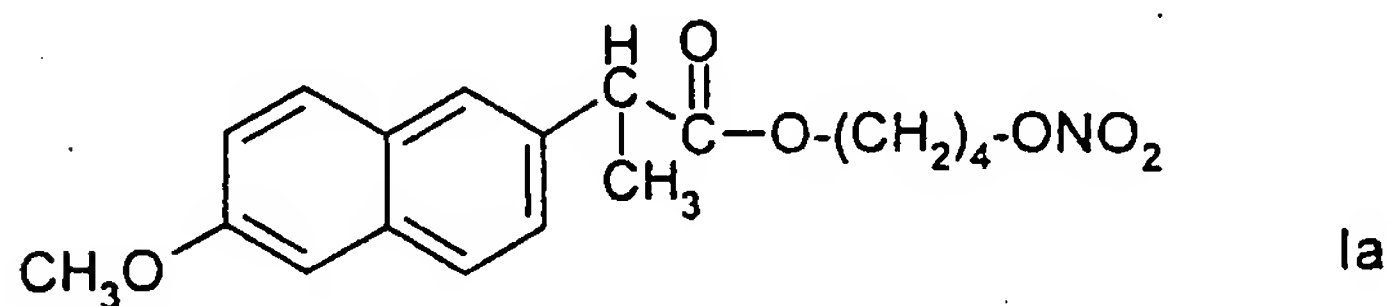
The examples below support that NO-releasing NSAIDs are active against *Helicobacter pylori*, and that the antibacterial activity is concentration dependent.

30

Example 1.

Strain: *Helicobacter pylori* reference strain NCTC 11 637 (National Type Culture
Collection, from Smittskyddsinstitutet in Solna, Sweden), an antibiotic
5 sensitive reference strain

Substance:

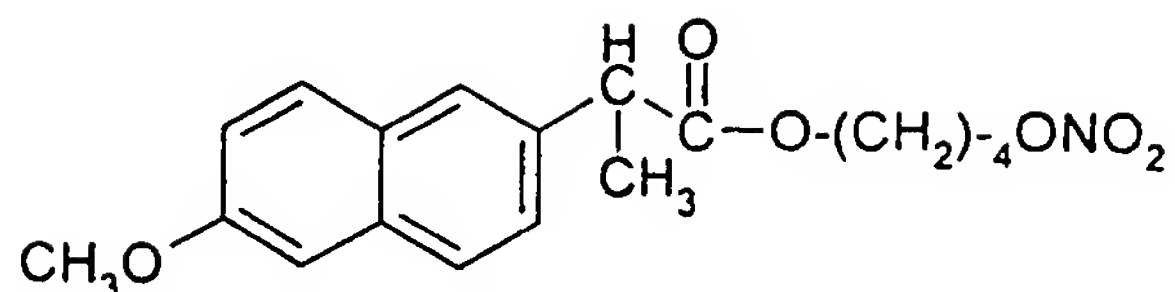


- 10 *Helicobacter pylori* was grown on blood agar plates, having a diameter of 90 mm, for three days under microaerophilic conditions at 37°C. The bacteria were suspended in PBS (phosphate buffer saline) to approximately 10^8 cfu/ml. Approximately 2 ml of the suspension was added to one agar plate and spread even on the surface of the agar. Overflow was removed with a syringe. Wells, like small holes, 3 mm in diameter, were
15 made in the agarplate by removing agar. Three wells per plate were made. A stock solution of a compound of the formula 1a having the concentration 100 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells. Result: The inhibition zone around each well was large, i.e. it was not possible to measure
20 the diameter of the zone.

Example 2.

Strain: *Helicobacter pylori* reference strain NCTC 11 637 (see Example 1), an
25 antibiotic sensitive reference strain

Substance:



Ia

The plates with the wells were prepared according to Example 1.

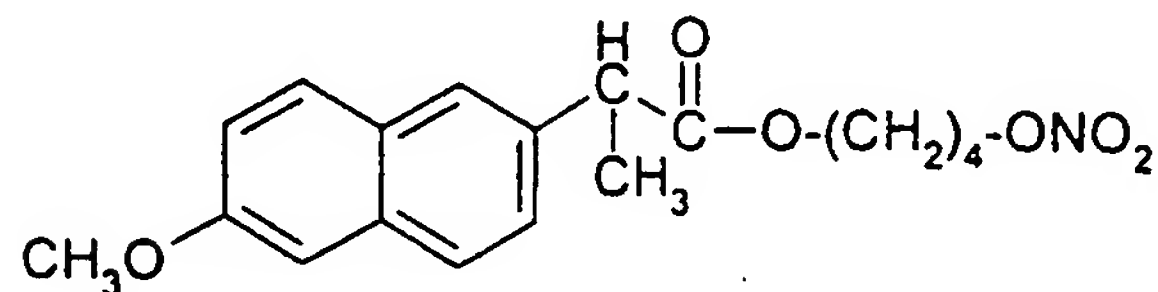
- 5 A stock solution of a compound of the formula Ia having the concentration 10 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

10 Result: The inhibition zone around each well was large, i.e. it was not possible to measure the diameter of the zone.

Example 3.

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive
15 reference strain (see Example 1)

Substance:



Ia

- 20 The plates with the wells were prepared according to Example 1.

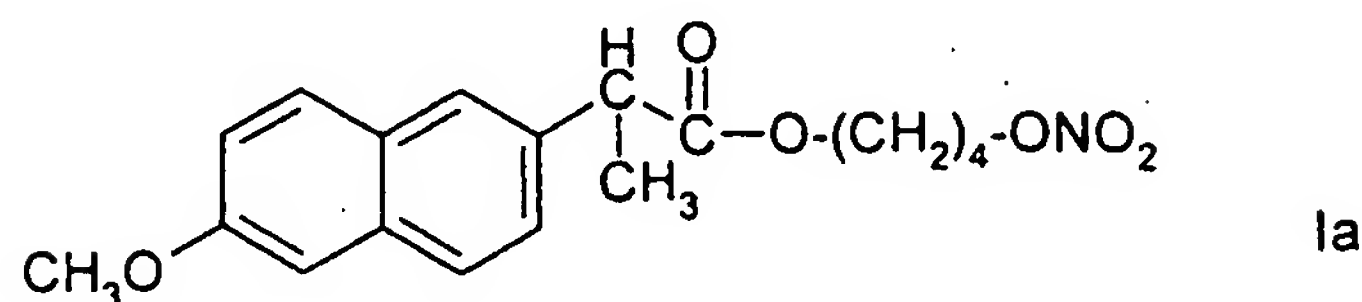
A stock solution of a compound of the formula Ia having the concentration 1 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

- 25 Result: The inhibition zone around each well was 13 mm.

Example 4.

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

5 Substance:



The plates with the wells were prepared according to Example 1.

10

A stock solution of a compound of the formula 1a having the concentration 100 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

15 Result: The inhibition zone around each well was 10.4 mm.

Comparative testsExample A

20

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Naproxen

25 The plates with the wells were prepared according to Example 1.

A stock solution of Naproxen having the concentration 10 000 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around the each well was 16.6 mm.

5

Example B

10 Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Naproxen

The plates with the wells were prepared according to Example 1.

15

A stock solution of Naproxen having the concentration 1000 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

20 Result: No inhibition zones around the wells were formed.

Example C

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive
25 reference strain (see Example 1)

Substance: Naproxen

The plates with the wells were prepared according to Example 1.

30 A stock solution of Naproxen having the concentration 100 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: No inhibition zones around the wells were formed.

5

Example D

10 Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: S-nitroso-N-acetyl-penicillamin (SNAP)

The plates with the wells were prepared according to Example 1.

15

A stock solution of SNAP with the concentration 10 000 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

20 Result: No inhibition zones around the wells were formed.

Example E

25 Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Di-methyl-sulphate-oxide (DMSO)

The plates with the wells were prepared according to Example 1.

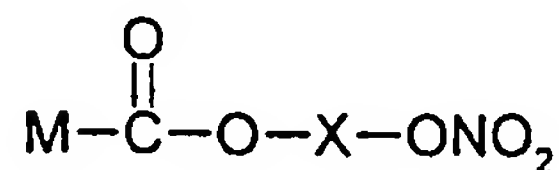
30 A solution of DMSO alone with the concentration 20 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: No inhibition zones around the wells were formed.

Claims

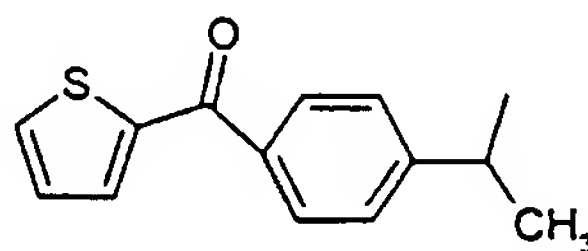
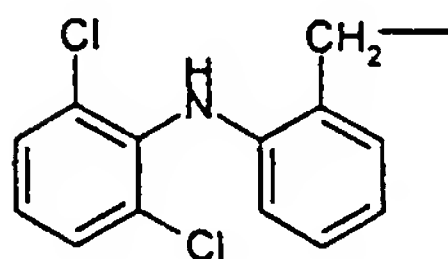
1. Use of a NO-releasing NSAID as well as a pharmaceutically acceptable salt or an enantiomer thereof, for the manufacture of a medicament for the treatment of bacterial
5 infections.
2. Use of a NO-releasing NSAID and an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer in the manufacture of pharmaceutical formulations intended for simultaneous, separate, or sequential
10 administration in the treatment of bacterial infections.
- 3 Use according to claim 1 or 2 wherein the NO-releasing NSAID is a compound of the formula I



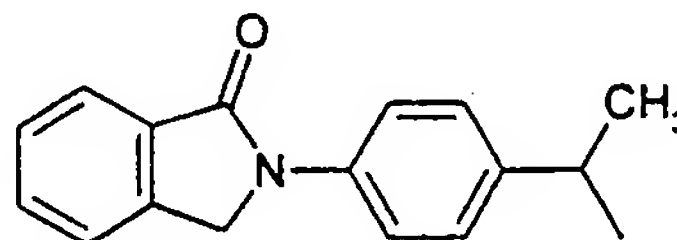
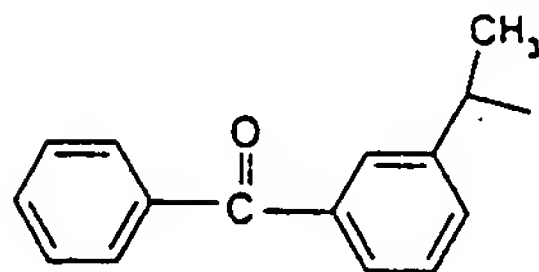
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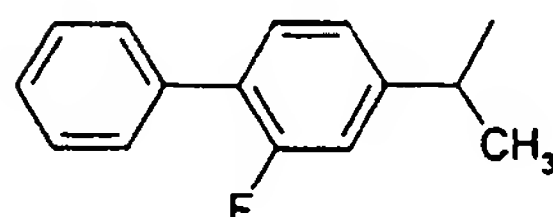
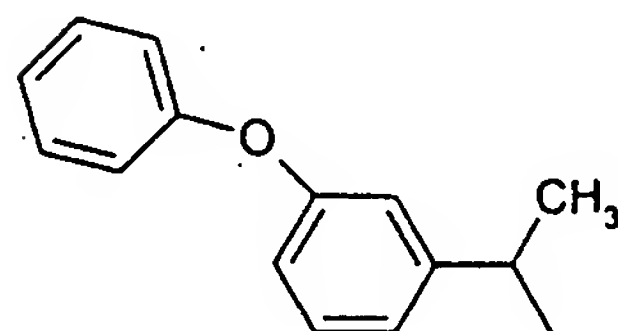
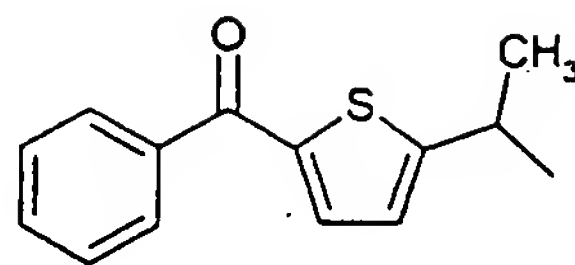
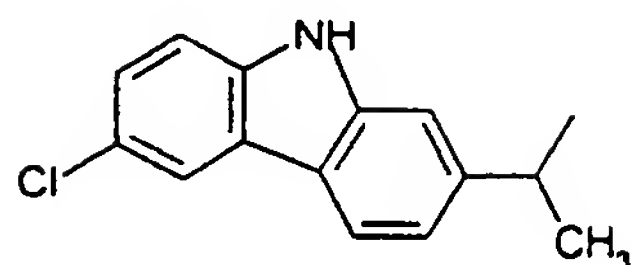
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wherein M is selected from anyone of

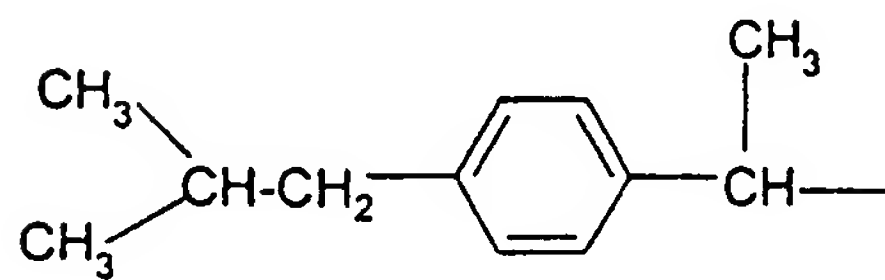
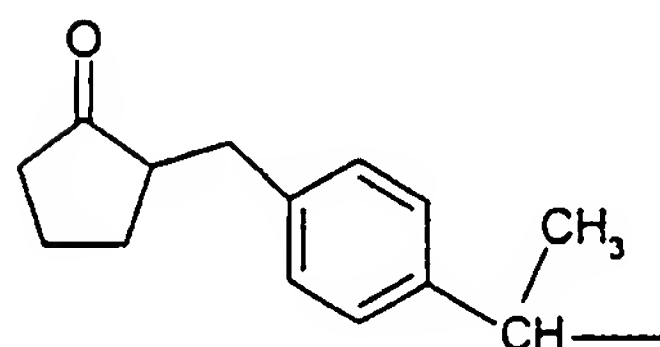
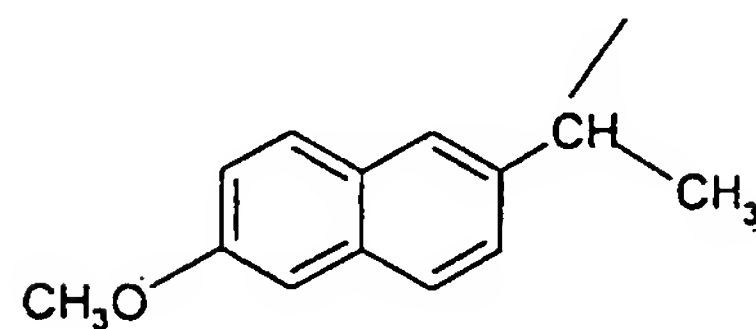
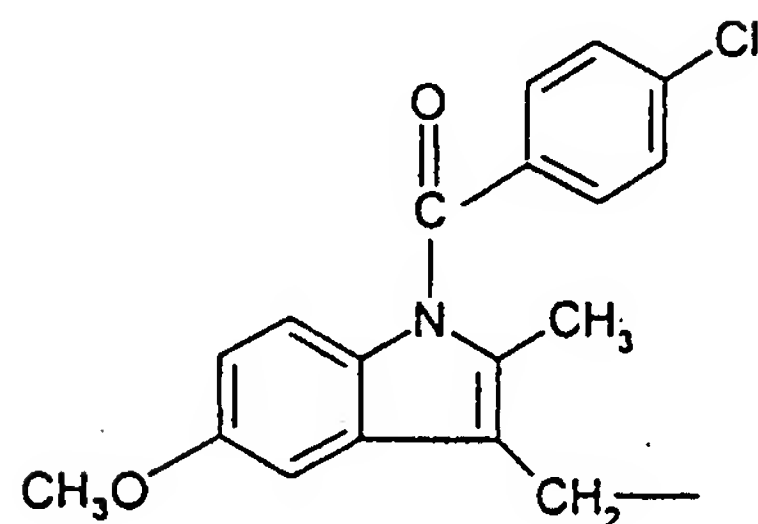
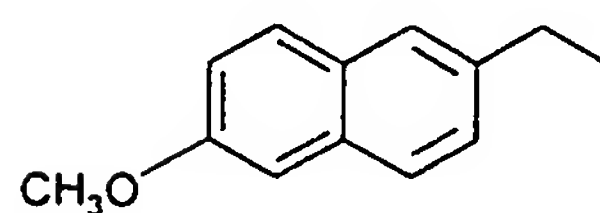
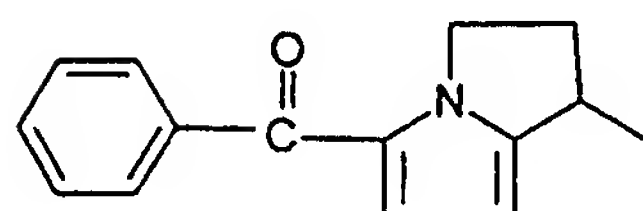


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10

and X is selected from

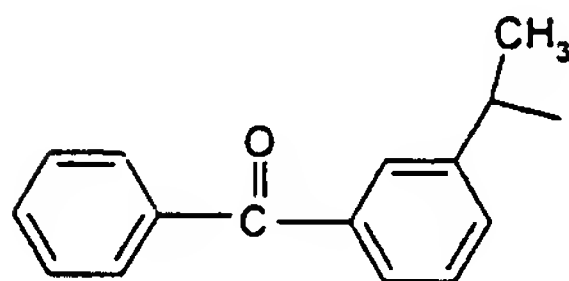
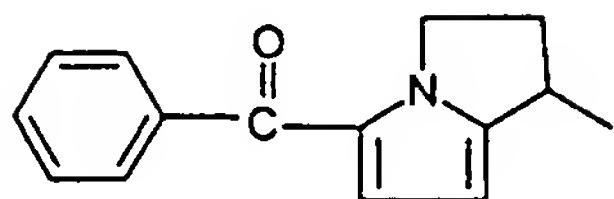
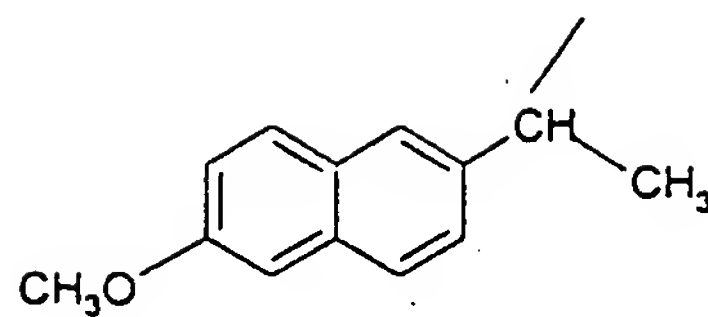
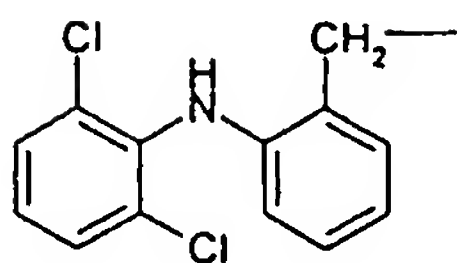
linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to 10;

$-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$,

15

or a pharmaceutically acceptable salt or enantiomer thereof.

4. Use according to claim 3 wherein M in formula I is selected from

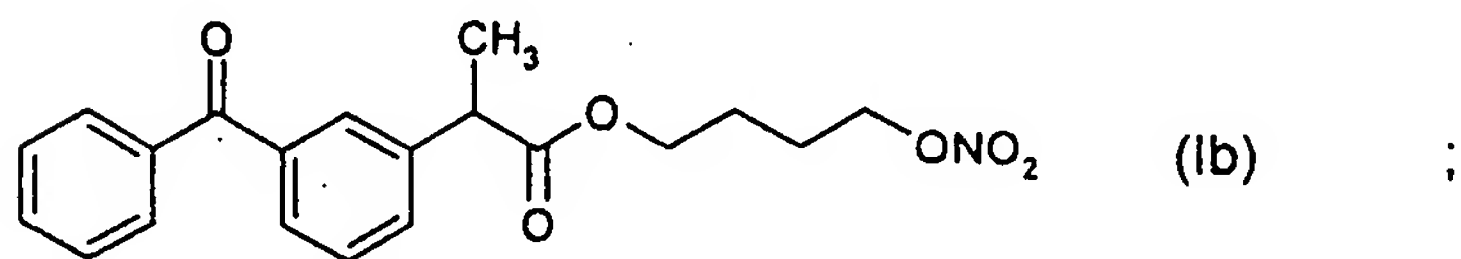
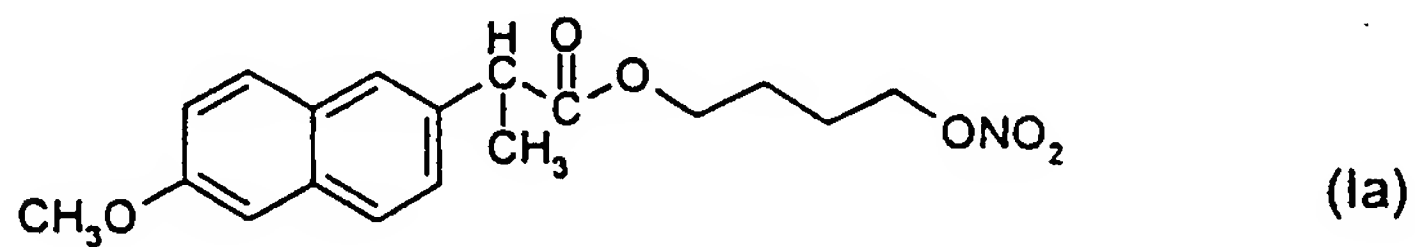


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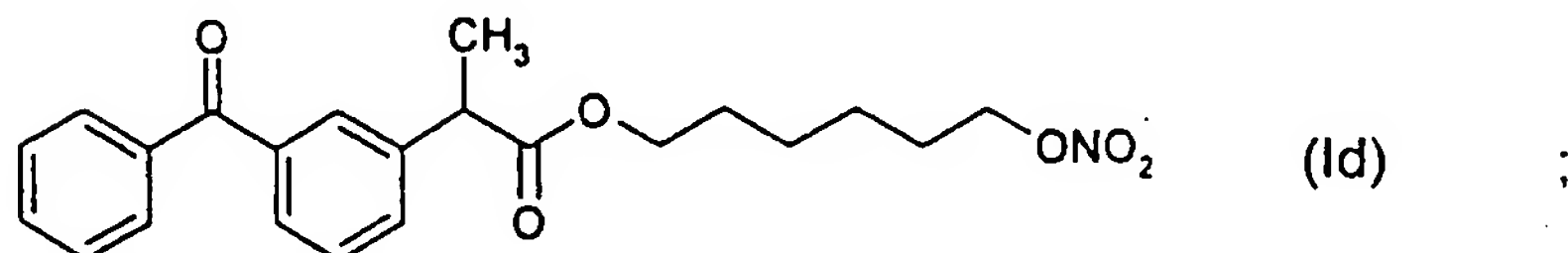
5. Use according to claim 3 or 4 wherein X in formula I is selected from linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6, $-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

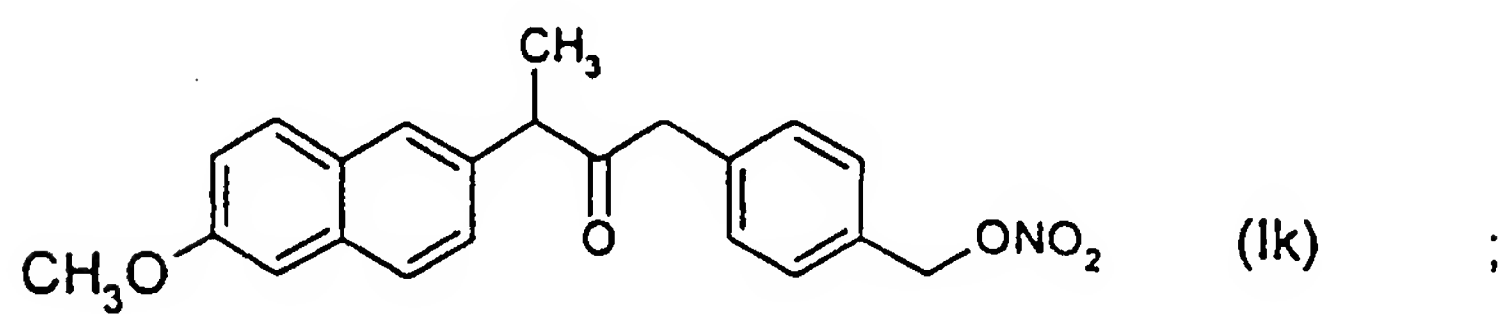
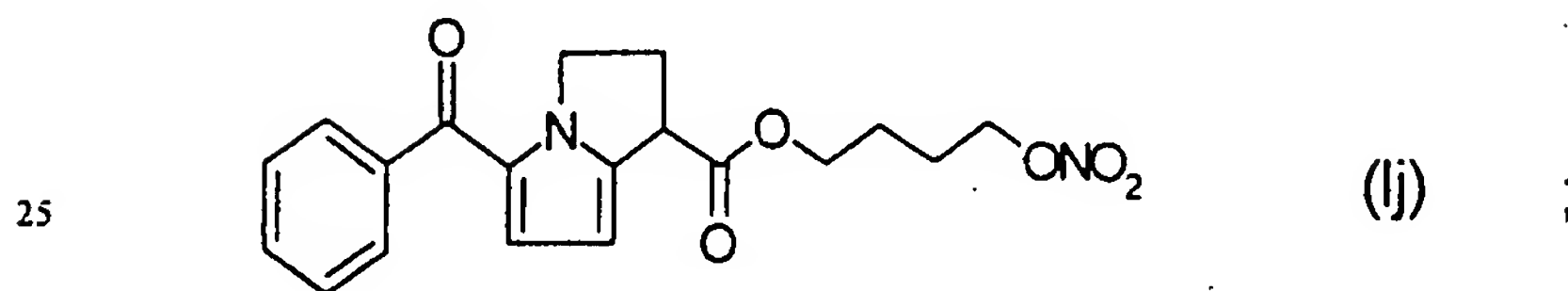
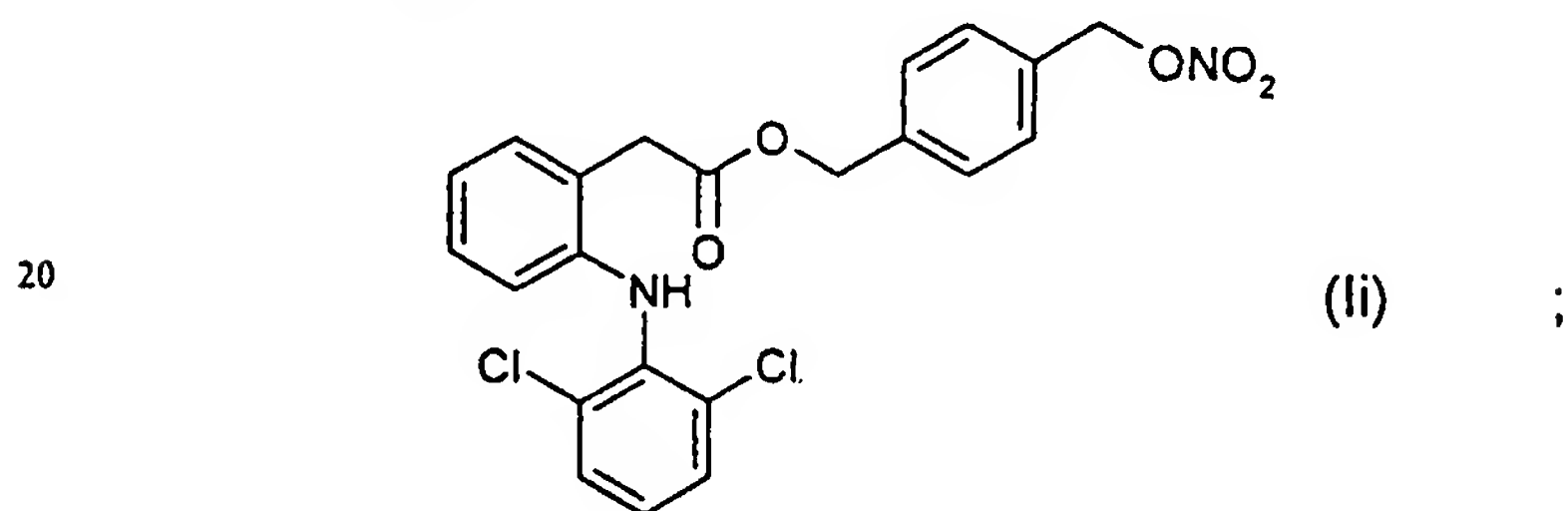
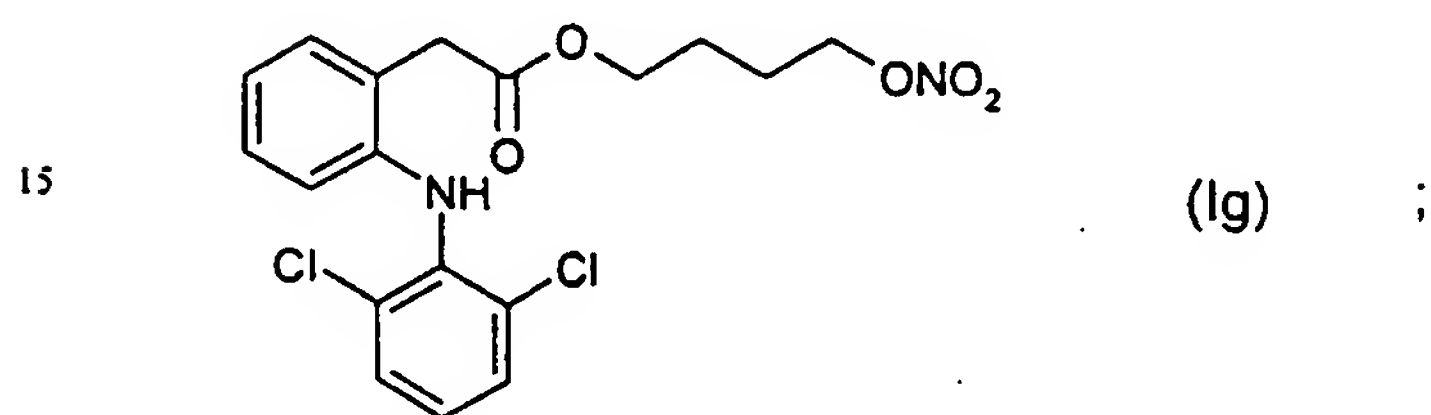
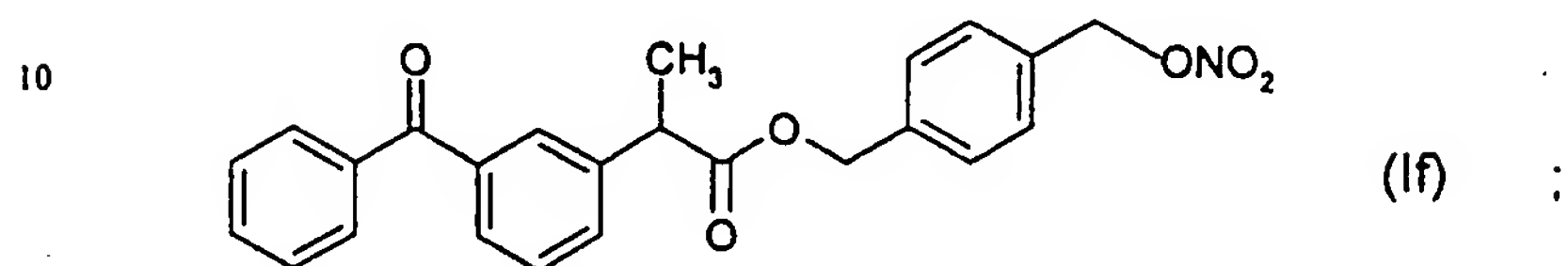
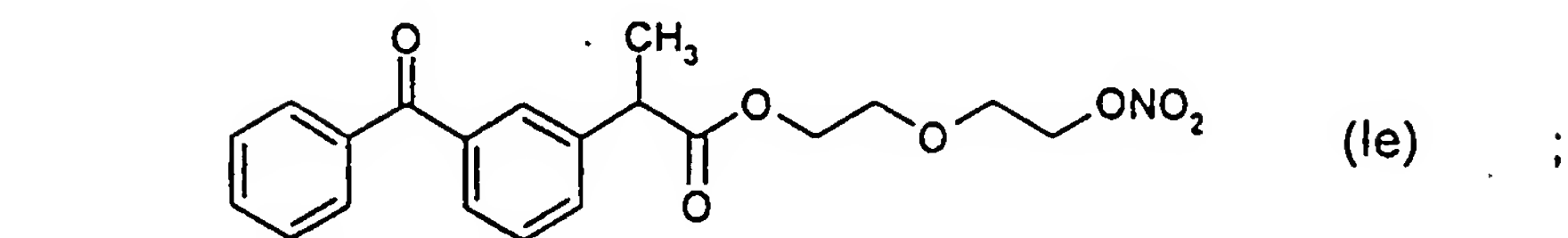
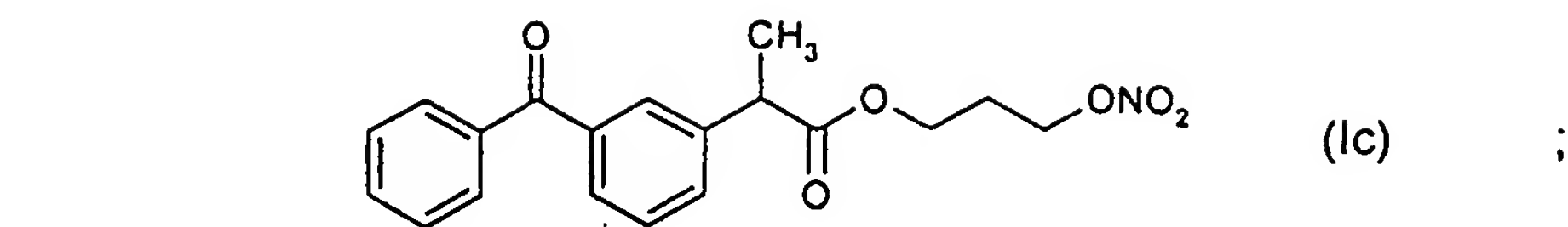
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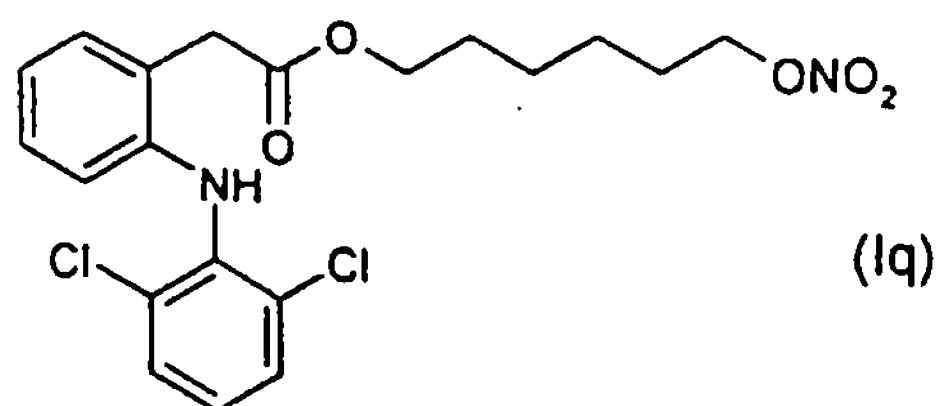
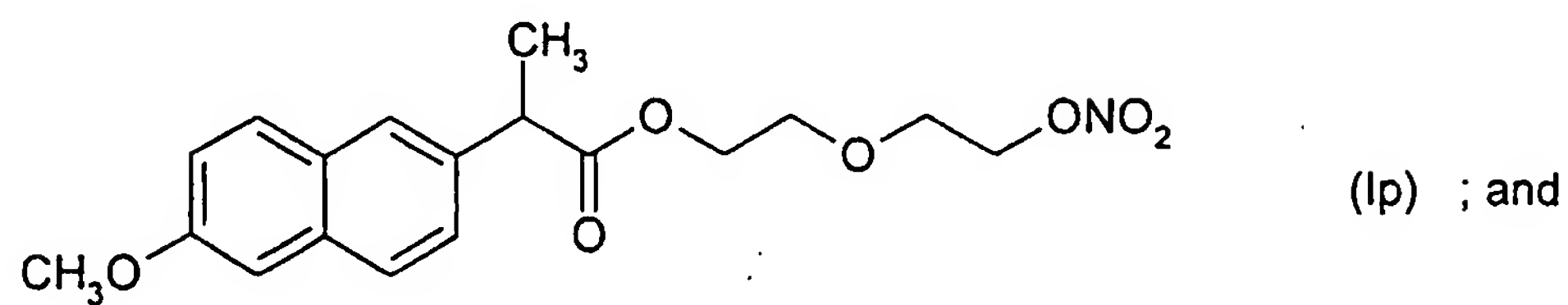
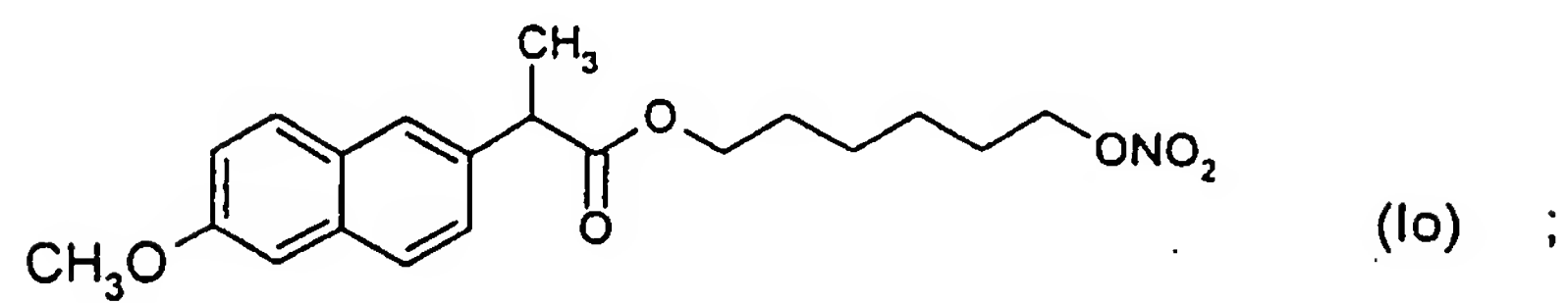
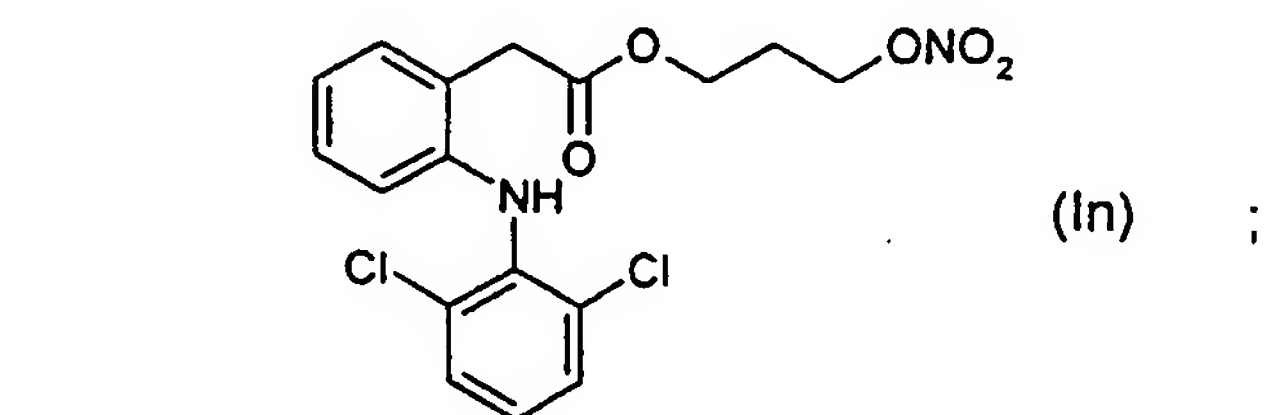
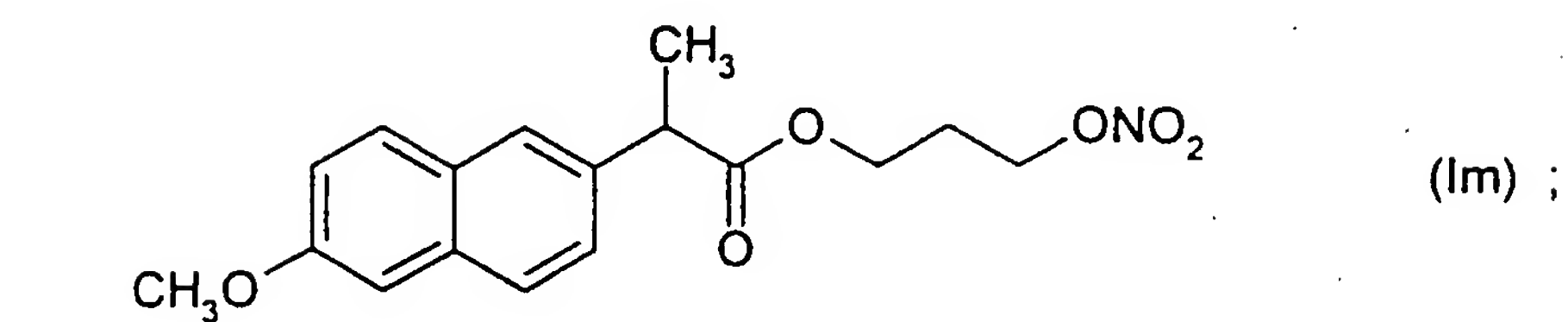
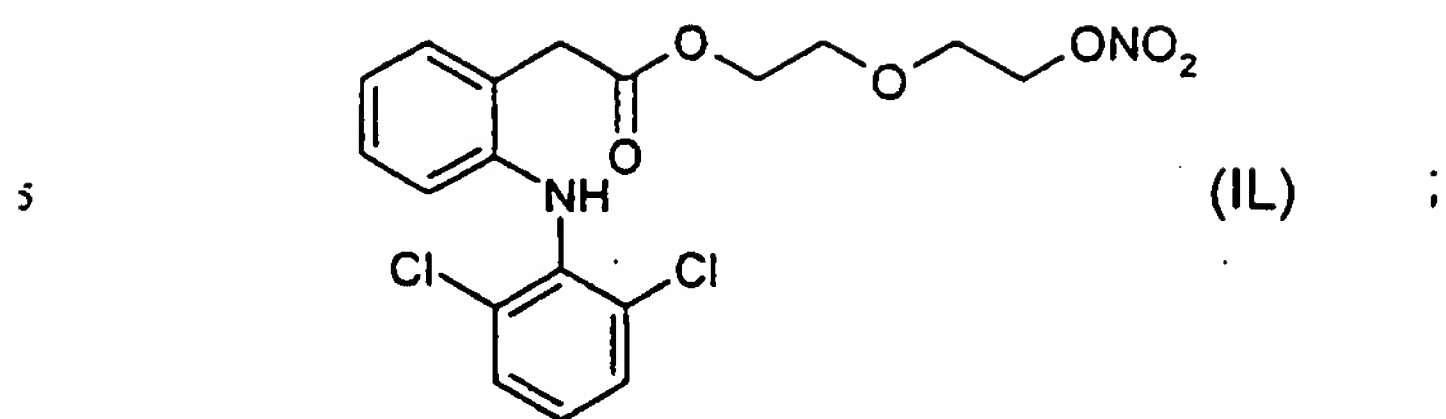
6. Use according to any one of claims 1 - 3 wherein the NO-releasing NSAID is a compound according to any one of the formulas Ia - Iq



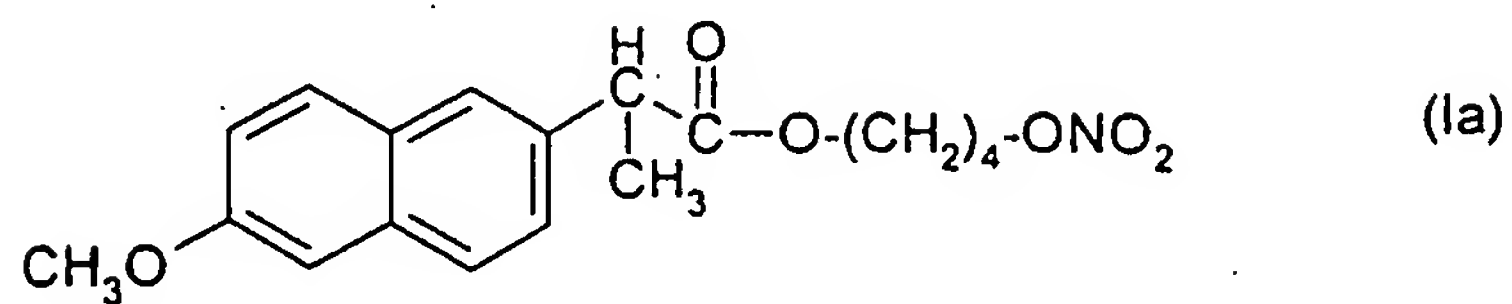
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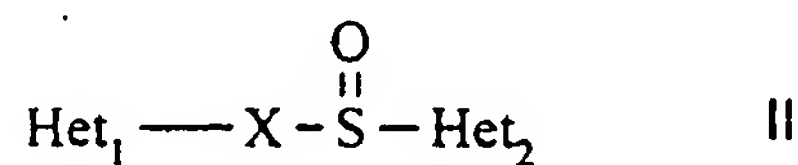




7. Use according to claim 6, wherein the NO-releasing NSAID is a compound of formula Ia

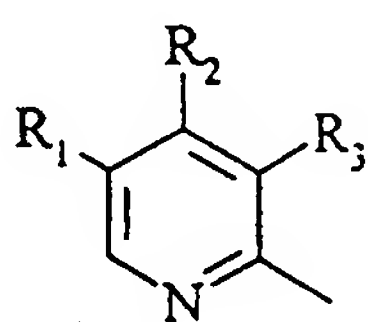


8. Use according to claim 2 wherein the acid susceptible proton pump inhibitor is a compound of the formula II

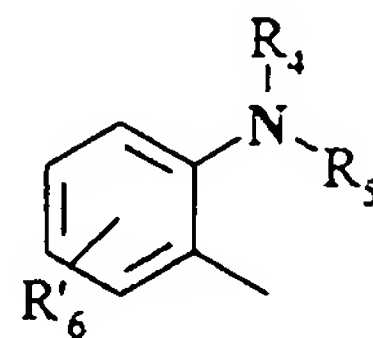


wherein

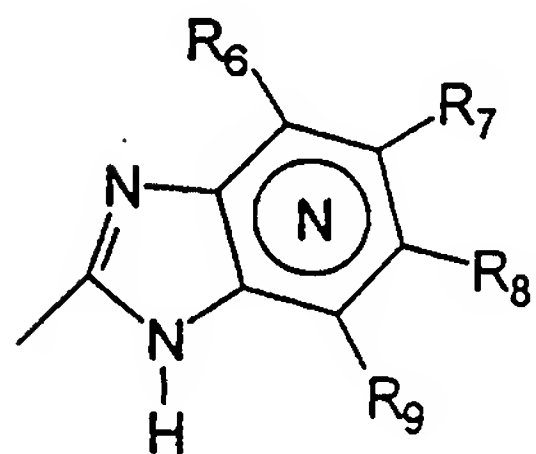
Het₁ is



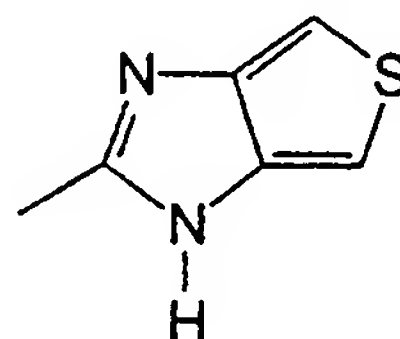
or



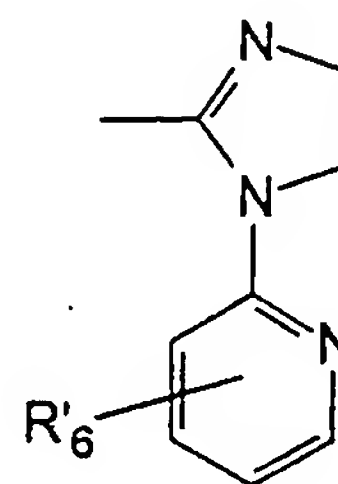
Het₂ is



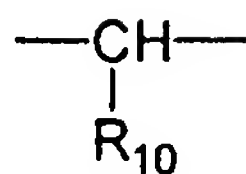
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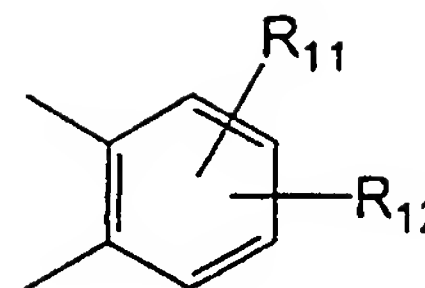
or



X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

R₆' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

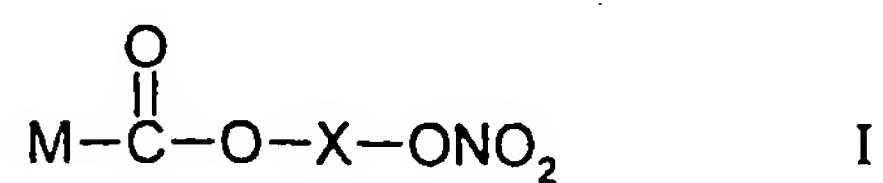
R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof, they may be branched or straight C₁ - C₉ - chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

9. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is selected from omeprazole, an alkaline salt thereof, (*S*)-omeprazole and an alkaline salt thereof.

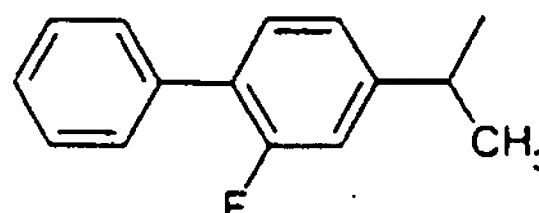
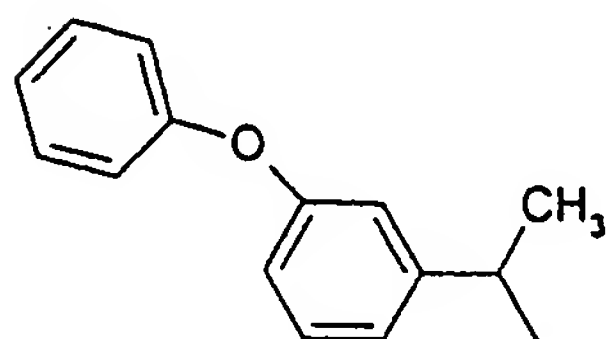
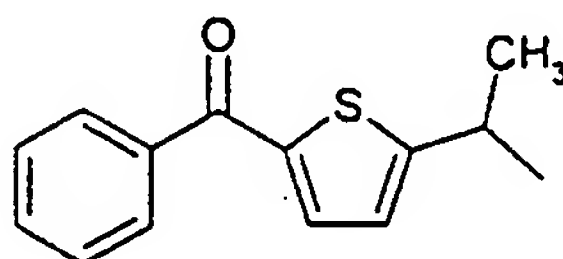
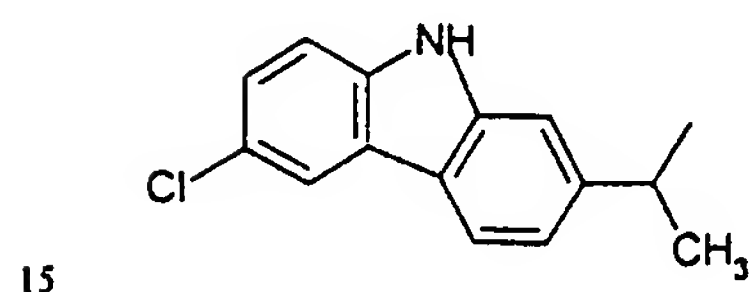
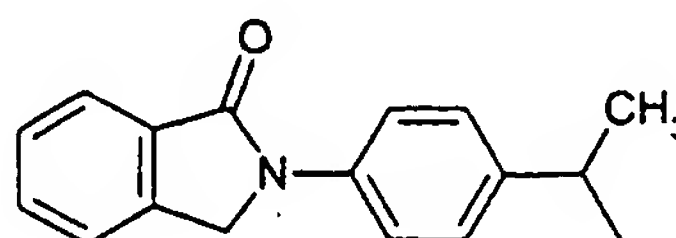
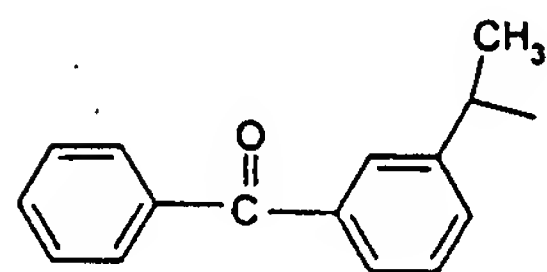
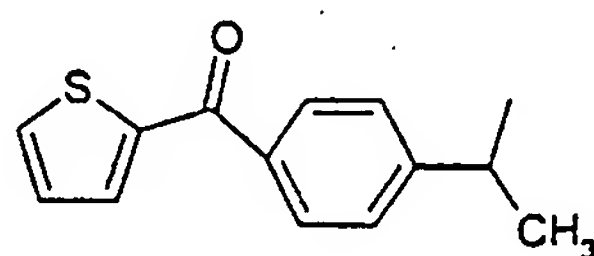
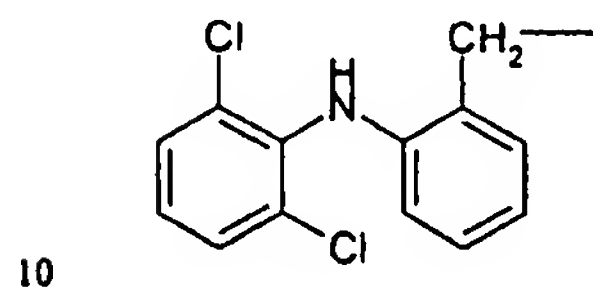
10. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is lansoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.
- 5 11. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is pantoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.
12. Use according to any one of the preceeding claims 1, to 11, wherein the bacterial
10 infection is caused or mediated by *Helicobacter pylori*.
13. Use according to claim 1, wherein the amount of NO-releasing NSAID in each dosage form is 0.5 – 5000 mg.
- 15 14. Use according to claim 13, wherein the amount of NO-releasing NSAID is 5 – 1000 mg.
15. Use according to claim 2, wherein the amount of NO-releasing NSAID is 0.5 – 5000 mg and the amount of proton pump inhibitor is 0.1 – 200 mg together in one dosage
20 form or in two separate dosage forms.
16. Use according to claim 15, wherein the amount of NO-releasing NSAID is 5 – 1000 mg and the amount of proton pump inhibitor is 10 – 80 mg.
- 25 17. A method for the treatment of a bacterial infection, comprising administering to a patient suffering from said bacterial infection, an effective amount of a NO-releasing NSAID or a pharmaceutically acceptable salt or an enantiomer thereof.
18. A method for the treatment of a bacterial infection, comprising simultaneously,
30 separately or sequentially administration to a patient suffering from said bacterial infection,

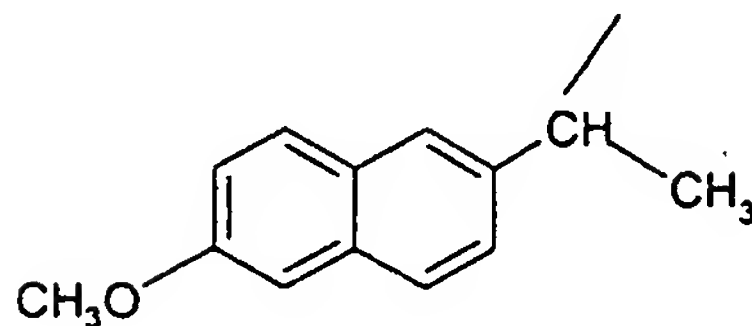
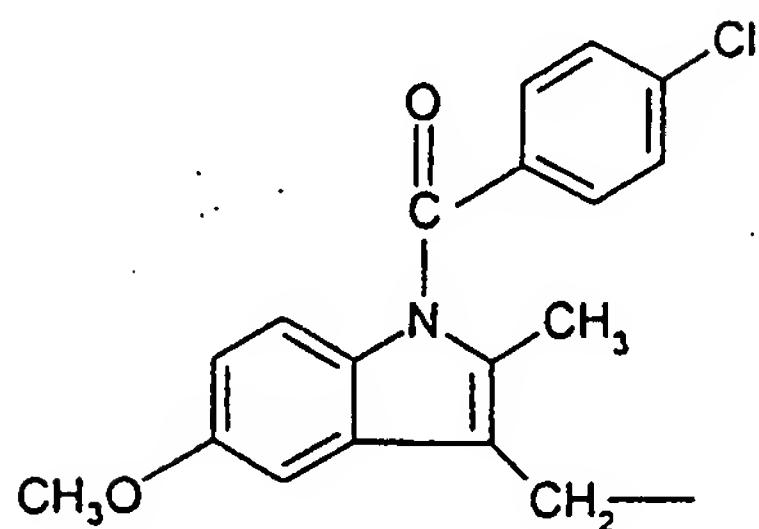
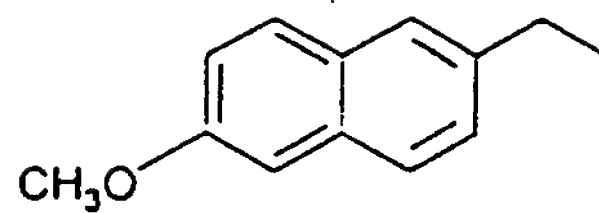
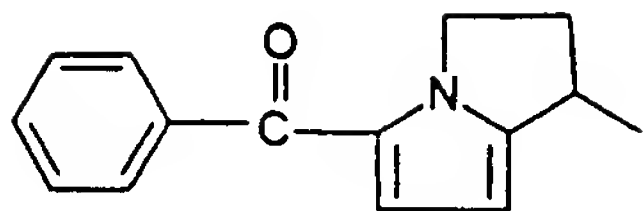
an effective amount of a NO-releasing NSAID and an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer.

19. A method according to claim 17 or 18 wherein the NO-releasing NSAID is a
s compound of the formula I

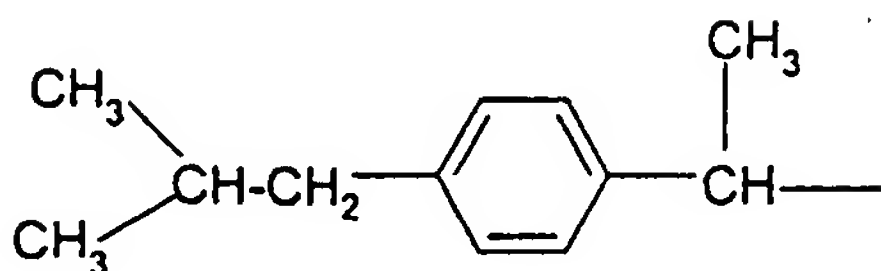


wherein M is selected from





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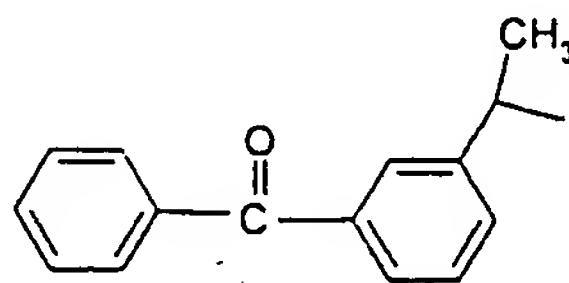
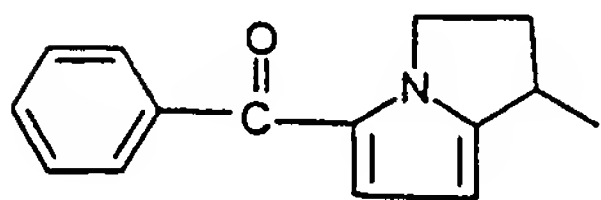
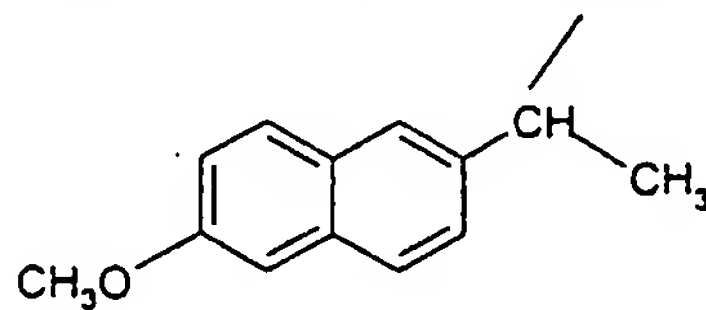
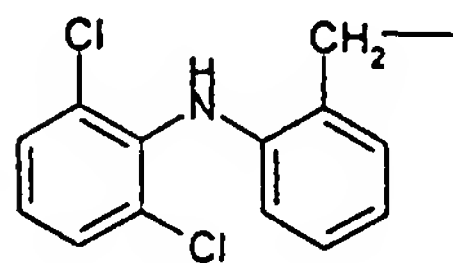


and X is selected from

- 10 linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to 10;
 $-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$,

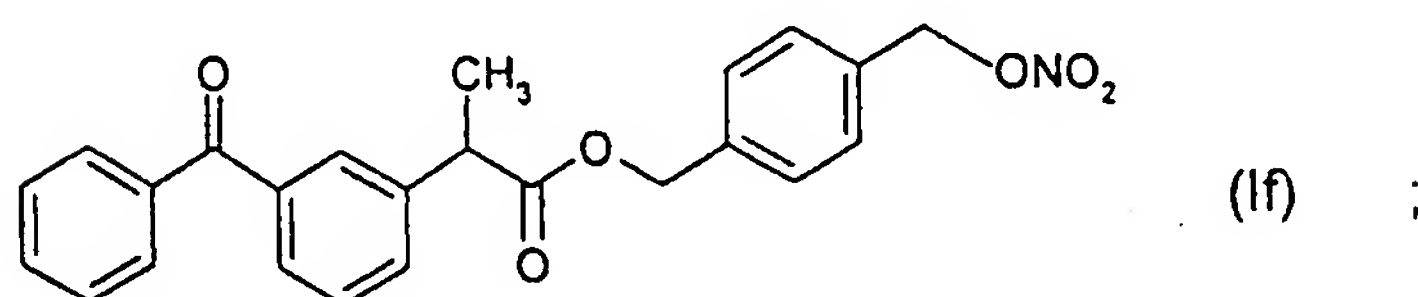
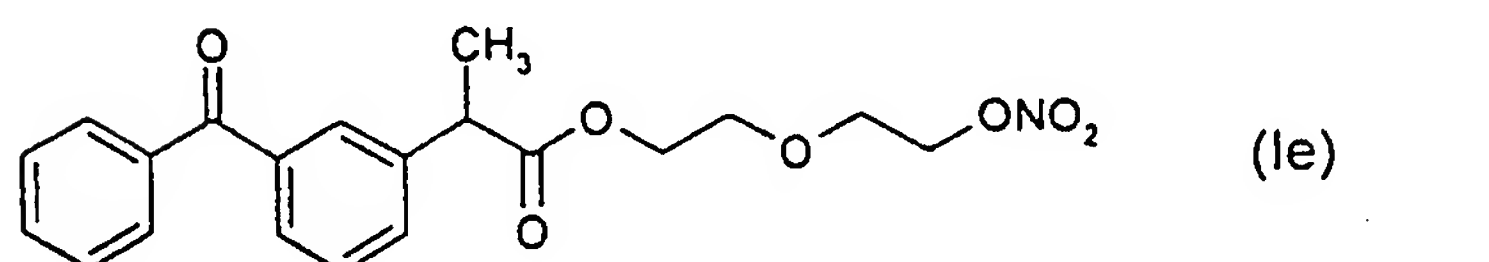
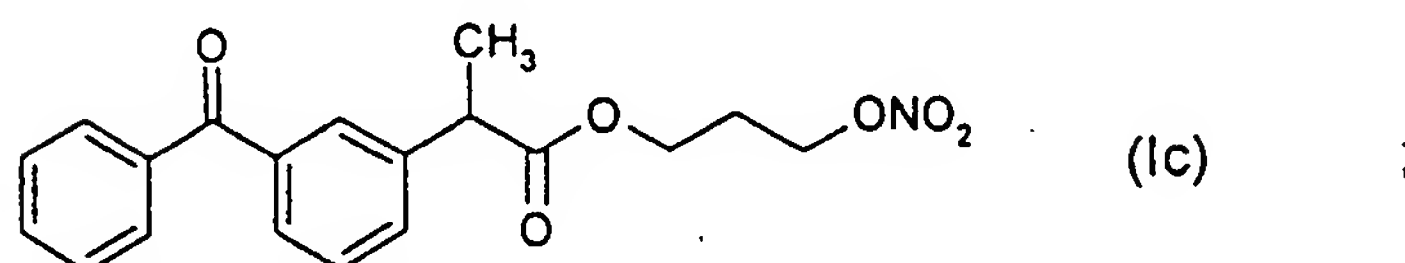
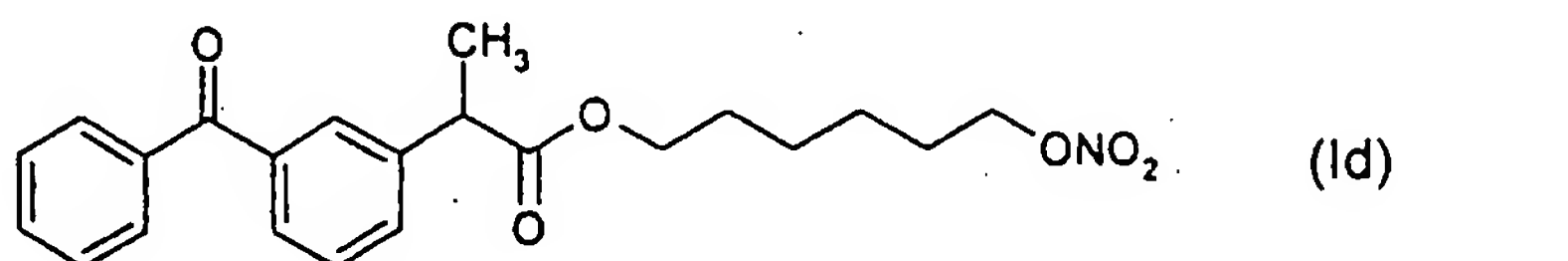
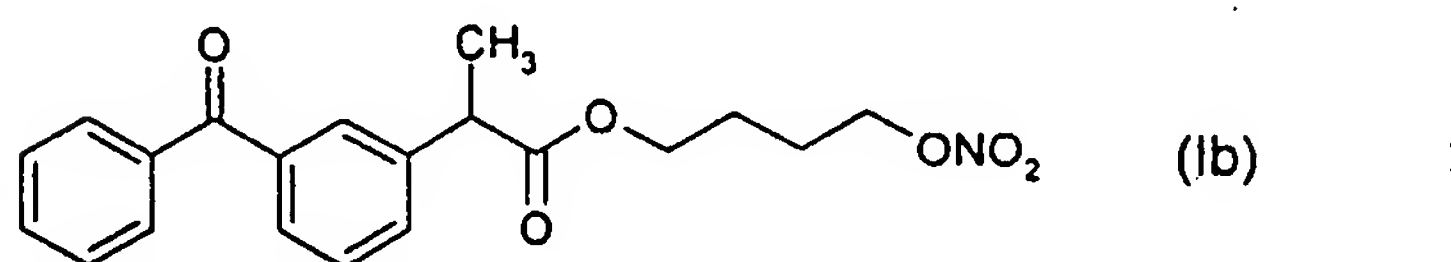
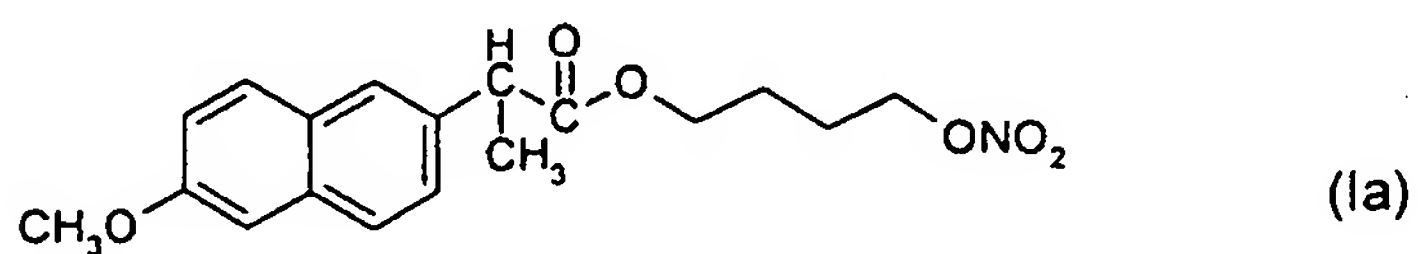
or a pharmaceutically acceptable salt or enantiomer thereof.

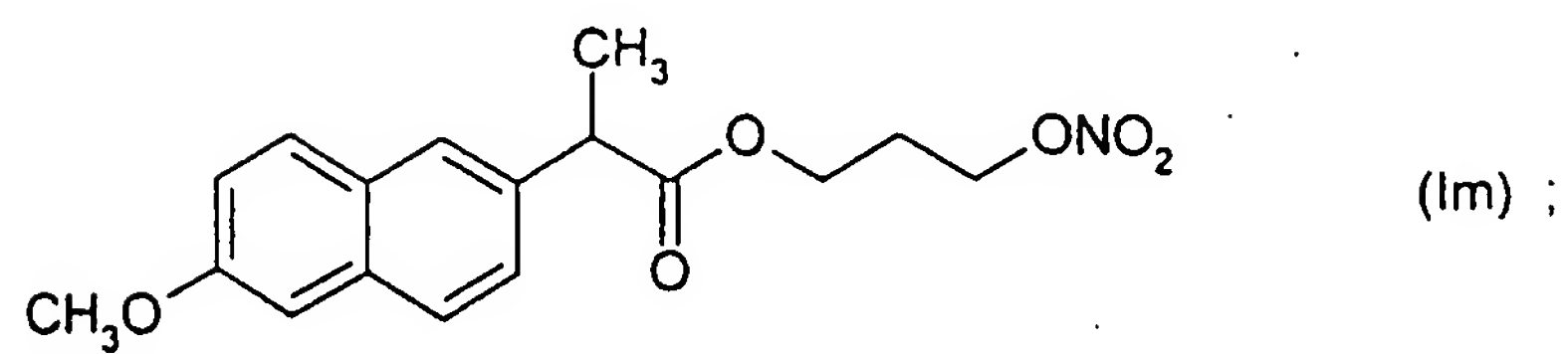
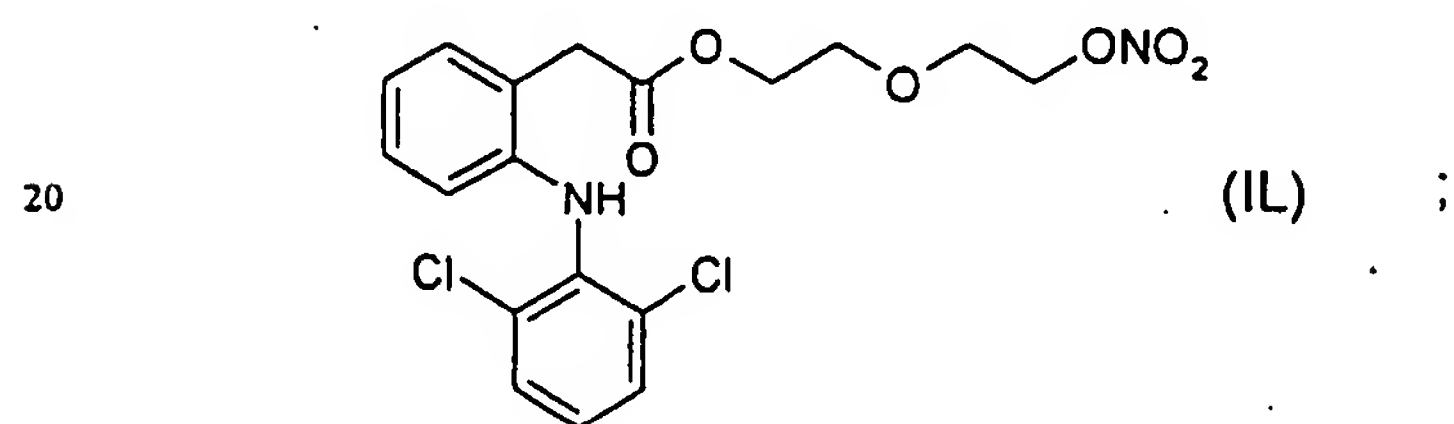
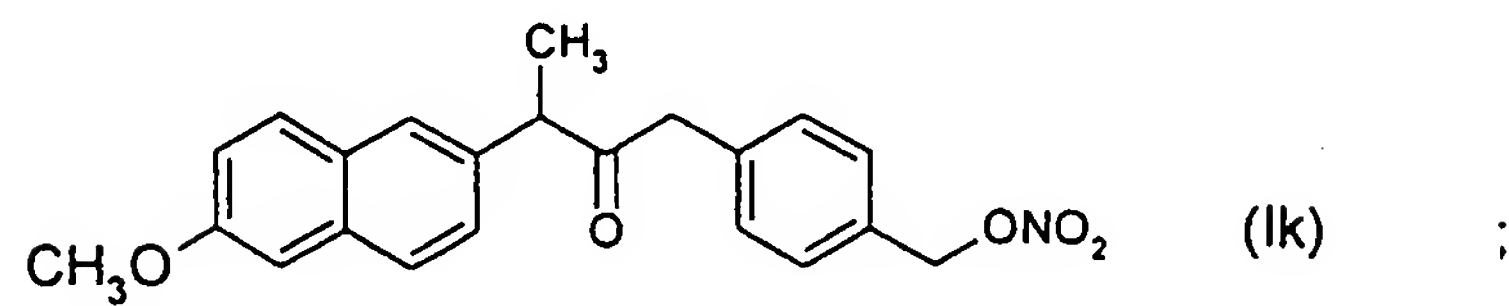
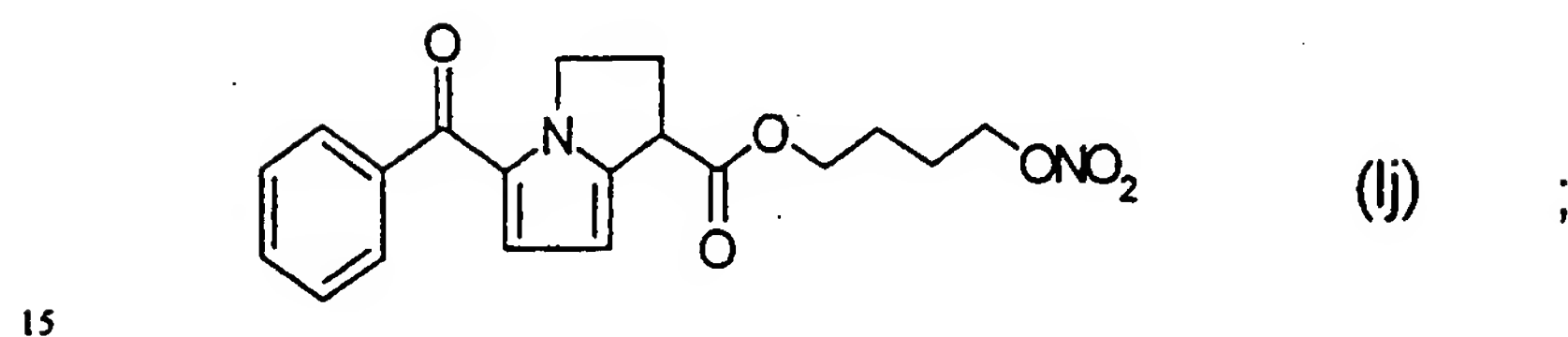
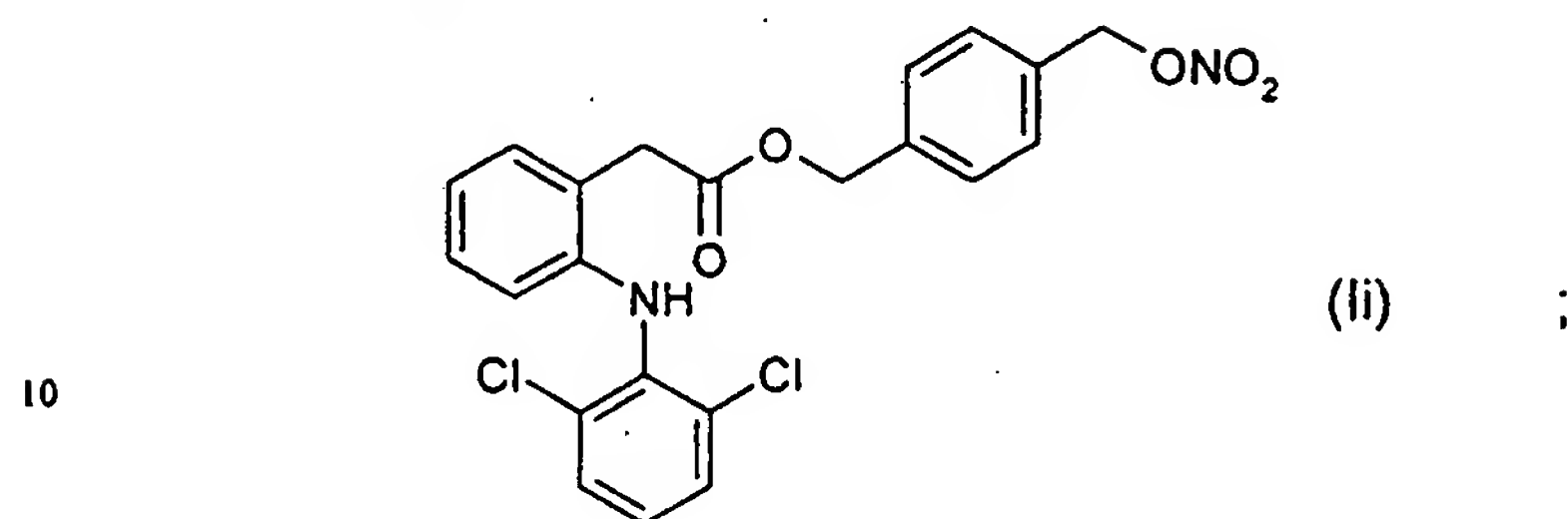
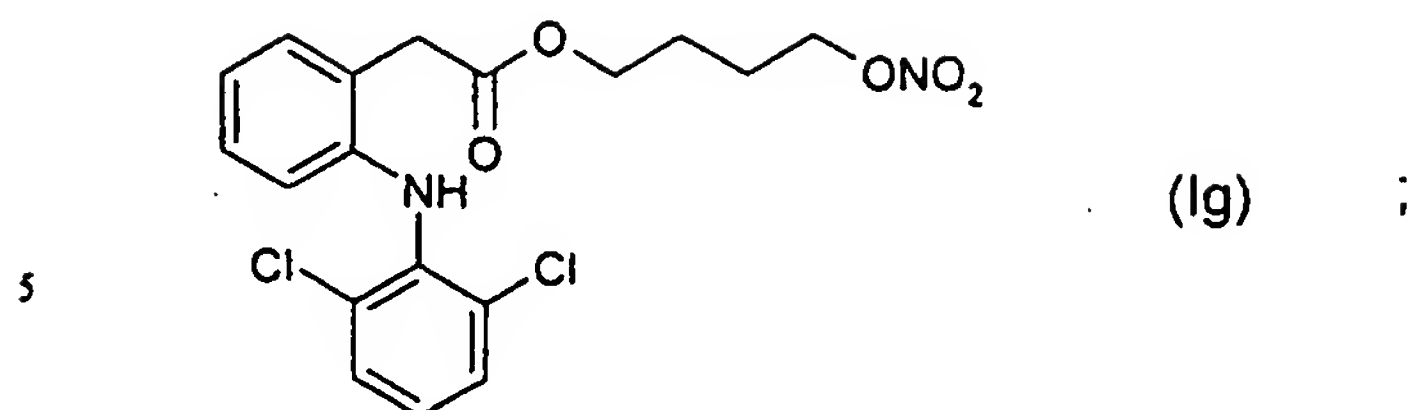
- 15 20. A method according to claim 19 wherein M in formula I is selected from

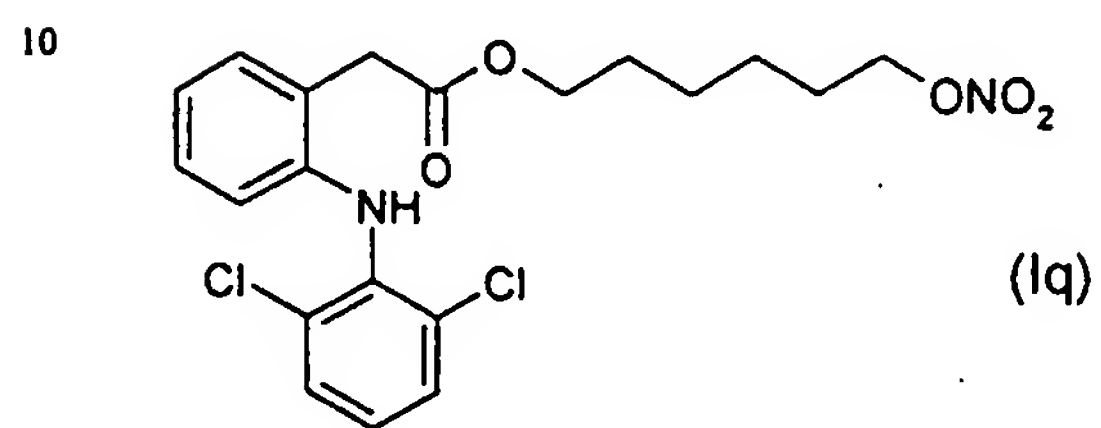
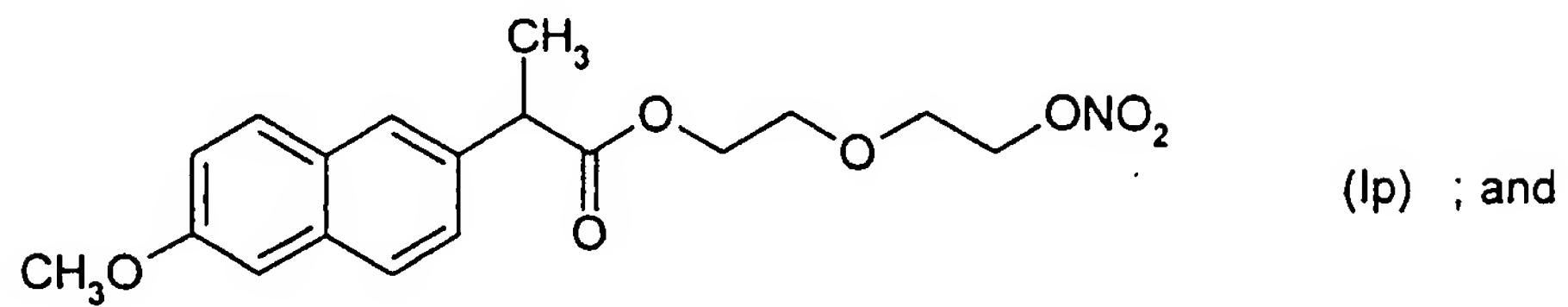
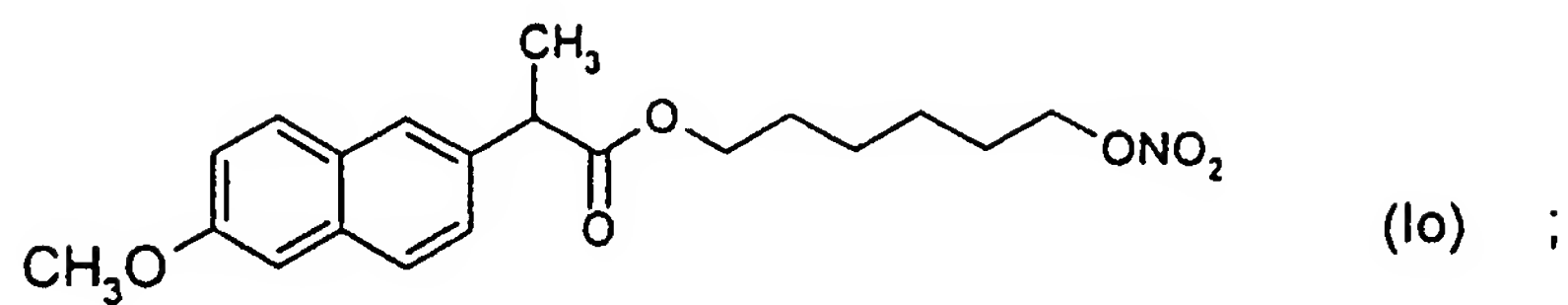
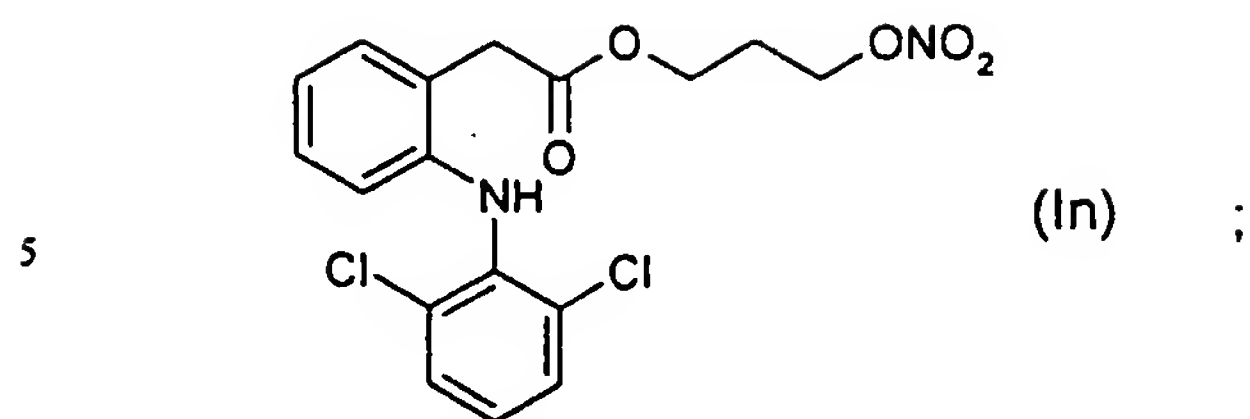


21. A method according to claim 19 or 20 wherein X in formula I is selected from linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6, $-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

22. A method according to any one of claim 17 – 19, wherein the NO-releasing NSAID is a compound according to any one of the formulas Ia - Iq

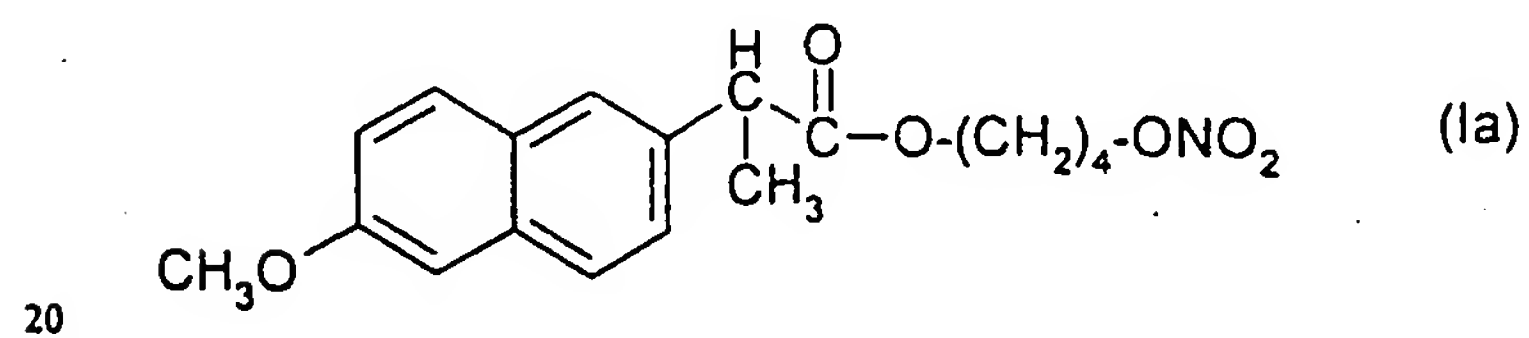




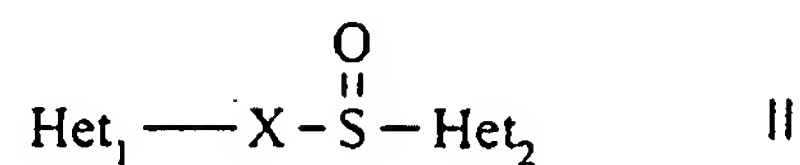


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23. A method according to claim 22, wherein the NO-releasing NSAID is a compound of formula Ia

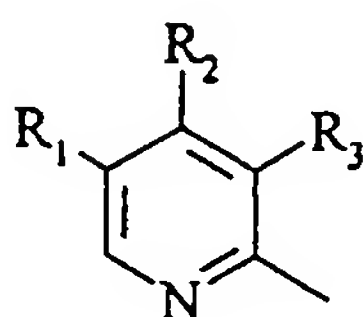


24. A method according to claim 18 wherein the acid susceptible proton pump inhibitor is a compound of the formula II

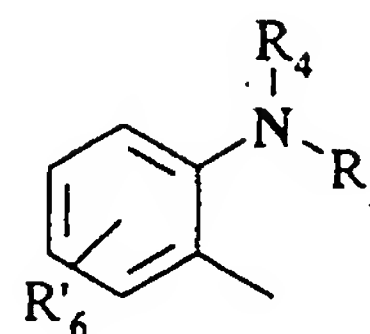


5 wherein

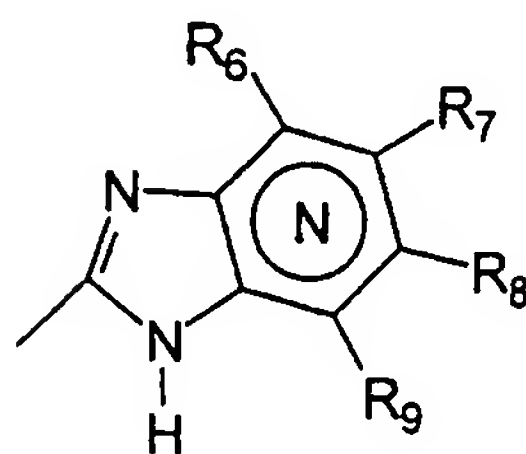
Het₁ is



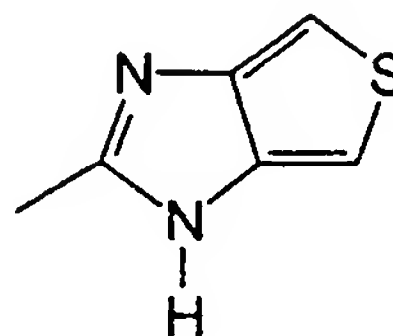
or



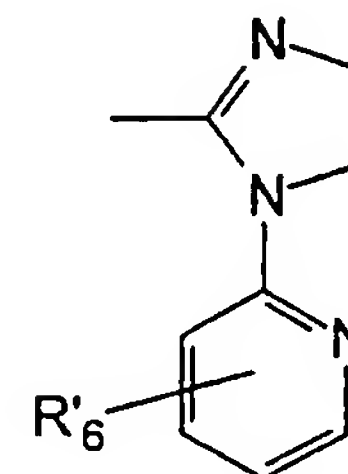
10 Het₂ is



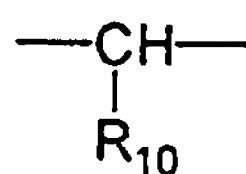
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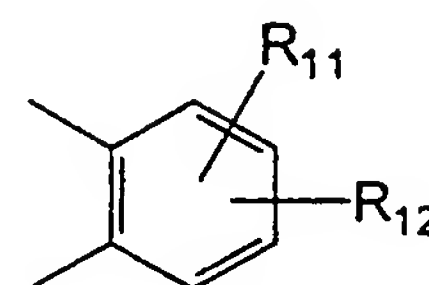
or



X =



or



wherein

15

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

20 R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

R₆' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

5

R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

10 R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof, they may be branched or straight C₁ - C₉ - chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

15

25. A method according to claim 24 wherein the acid susceptible proton pump inhibitor is selected from omeprazole, an alkaline salt thereof, (*S*)-omeprazole and an alkaline salt thereof.

20 26. A method according to claim 24 wherein the acid susceptible proton pump inhibitor is lansoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

25 27. A method according to claim 24 wherein the acid susceptible proton pump inhibitor is pantoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

28. A method according to any one of the preceeding claims 17 to 27, wherein the bacterial infection is caused or mediated by *Helicobacter pylori*.

30

29. A method according to claim 17, wherein the amount of NO-releasing NSAID in each dosage form is 0.5 – 5000 mg.

30. A method according to claim 29, wherein the amount of NO-releasing NSAID is
5 5 – 1000 mg.

31. A method according to claim 18, wherein the amount of NO-releasing NSAID is 0.5 – 5000 mg and the amount of proton pump inhibitor is 0.1 – 200 mg together in one dosage form or in two separate dosage forms.

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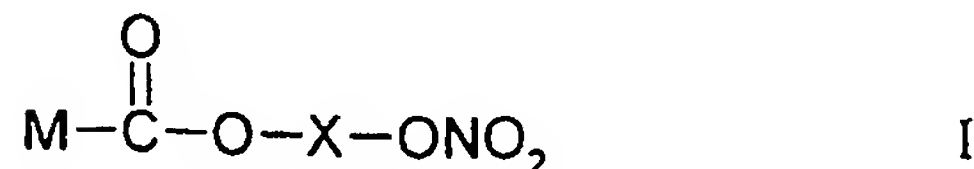
32. A method according to claim 31, wherein the amount of NO-releasing NSAID is 5 – 1000 mg and the amount of proton pump inhibitor is 10 – 80 mg.

33. A pharmaceutical formulation suitable for use in the treatment of bacterial
15 infections, comprising a NO-releasing NSAID or a pharmaceutically acceptable salt or an enantiomer thereof as active agent.

34. A pharmaceutical formulation suitable for use in the treatment of bacterial infections, comprising a NO-releasing NSAID and an acid susceptible proton pump
20 inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer as active agents.

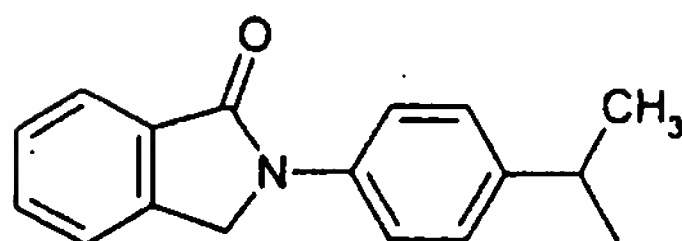
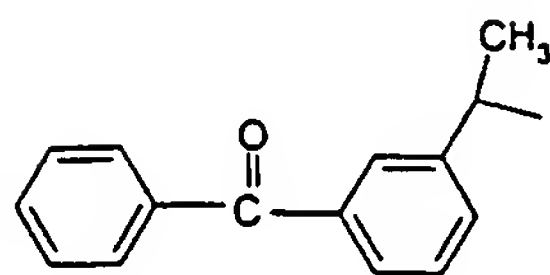
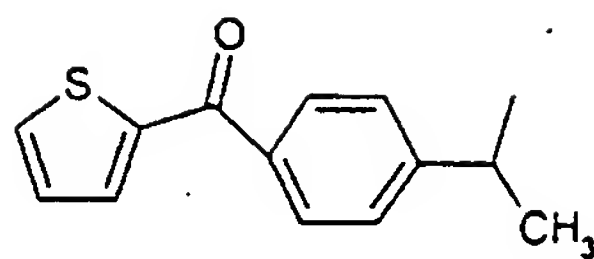
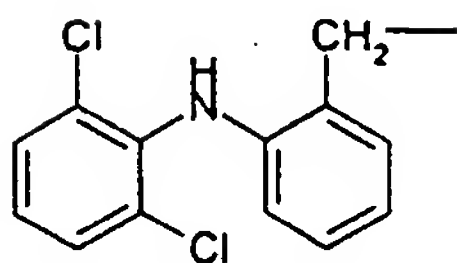
35. A pharmaceutical formulation according to claim 25 or 26 wherein the NO-releasing NSAID is a compound of the formula I

25

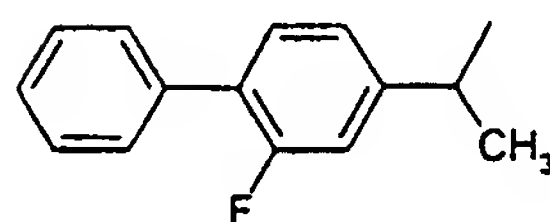
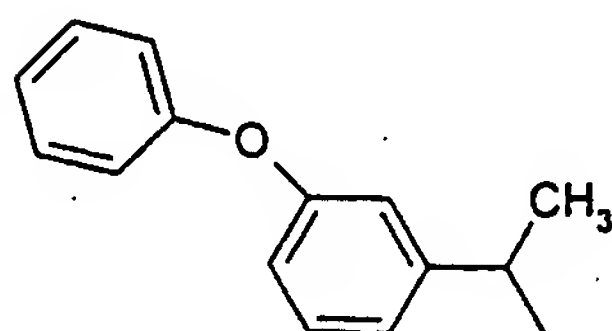
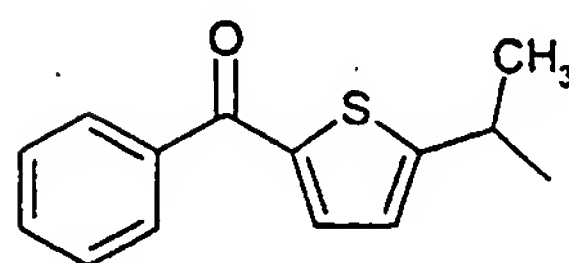
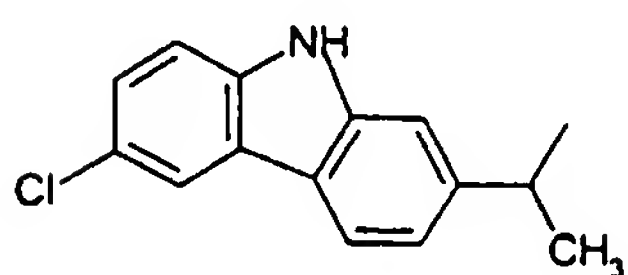


wherein M is selected from

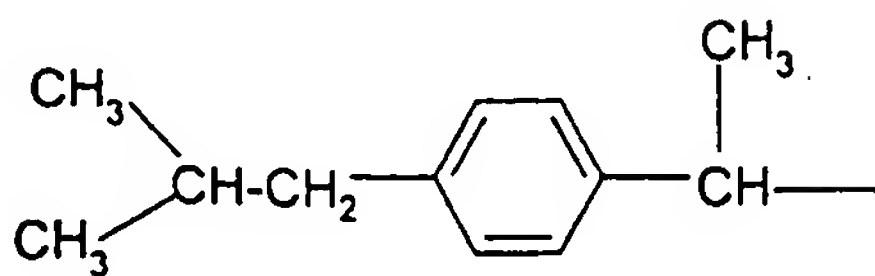
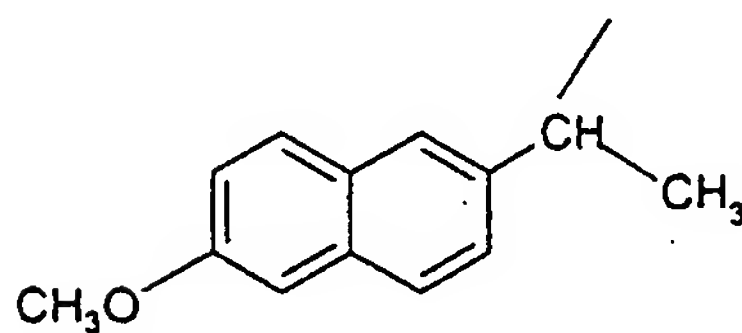
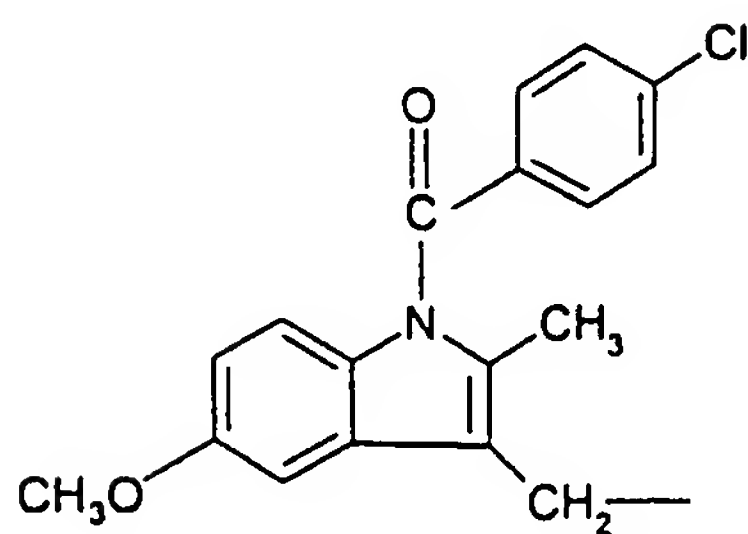
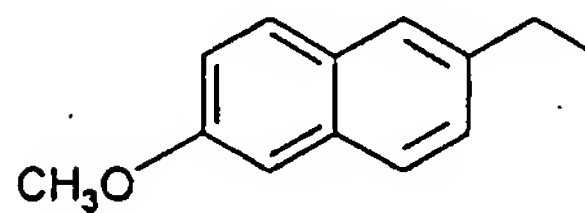
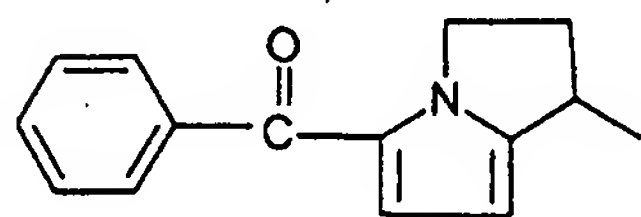
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10



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and X is selected from

linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to 10;

$-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$;

5

or a pharmaceutically acceptable salt or enantiomer thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/01071

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/04, A61K 31/196, A61K 31/33, A61P 1/04, A61P 31/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1999:500417, Document no. 131:255524, Yanaka, Akinori: "Role of nitric oxide in the pathogenesis of gastrointestinal diseases"; & Ensho (1999), 19 (3), 129-135 --	1-32
X	Pharmacol Ther, Volume 11, 1997, N.M. DAVIES et al, "NO-naproxen vs. naproxen: ulcerogenic, analgesic and anti-inflammatory effects" page 69 - page 79 --	1-32
X	WO 9967210 A1 (DUKE UNIVERSITY MEDICAL CENTER), 29 December 1999 (29.12.99), see part. page 3, line 18-19, page 15, line 17-20 --	1-32

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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Date of the actual completion of the international search

18 Sept 2000

Date of mailing of the international search report

20 -09- 2000

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Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Eva Johansson/GH
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/01071

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 9509831 A1 (NICOX LIMITED), 13 April 1995 (13.04.95) --	33-35
X	WO 9412463 A1 (HCT-HEALTH CARE TRADING LTD.), 9 June 1994 (09.06.94) --	33-35
X	WO 9530641 A1 (NICOX LIMITED), 16 November 1995 (16.11.95) --	33-35
A	WO 9731654 A1 (NICOX S.A.), 4 Sept 1997 (04.09.97) --	1-35
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01/08/00

International application No.

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01/08/00

International application No.

PCT/SE 00/01071

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INTERNATIONAL SEARCH REPORT

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01/08/00

International application No.

PCT/SE 00/01071

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 January 2001 (04.01.2001)

PCT

(10) International Publication Number
WO 01/00563 A1

- (51) International Patent Classification⁷: C07C 203/04, A61K 31/21
- (74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni, 2, I-20129 Milano (IT).
- (21) International Application Number: PCT/EP00/05723
- (81) Designated States (*national*): AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA.
- (22) International Filing Date: 21 June 2000 (21.06.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (30) Priority Data:
MI99A001402 24 June 1999 (24.06.1999) IT
- (71) Applicant (*for all designated States except US*): NICOX S.A. [FR/FR]; 45, Avenue Kléber, F-75116 Paris (FR).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): BENEDINI, Francesca [IT/IT]; Via Padova, 286, I-20100 Milano (IT). ANTOGNAZZA, Patrizia [IT/IT]; Via A. Volta, 1, I-22070 Locate Varesino (IT).

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/00563 A1

(54) Title: AMORPHOUS NITRIC ESTERS AND THEIR PHARMACEUTICAL COMPOSITIONS

(57) Abstract: Compounds of formula A-X₁-ONO₂ (I) in a partially or completely amorphous form and pharmaceutical compositions thereof.

AMORPHOUS NITRIC ESTERS AND THEIR PHARMACEUTICAL COMPOSITIONS

The present invention relates to nitroxy derivatives of the hydroxybenzoic acid in a modified physical form, and the pharmaceutical formulations thereof, said derivatives having general formula



wherein A is an hydroxybenzoic acid derivative as defined hereunder, X_1 is a linking bivalent radical as defined hereunder, said formulations capable to induce in very short times, of the order of 2-2.5 hours, the plasmatic concentration peak of the hydroxybenzoic acid derivative, defined as A.

The compositions of the invention can be used to prepare oral dosage forms suitable to induce a fast beginning of the pharmacological effect.

As well known the pharmacologically active substances when administered per os produce a systemic effect only after having undergone an absorption process through the gastroenteric duct walls. The drug absorption process is a complex phenomenon which depends on various factors, among which drug liposolubility and hydrosolubility. It is difficult to theoretically foresee, in practice it is impossible to know which is the optimal combination of these factors to obtain the maximum absorption peak of the active principle in short times, of about

2-2.5 hours at most.

Generally the therapeutic effect of a drug which shows its activity by systemic route when administered per os depends, in particular, on the following factors:

- drug absorption through the gastrointestinal wall,
- concentration in the hematic fluid,
- possible interaction with the target tissue.

In particular for the drugs having an antiinflammatory and analgesic activity, an essential feature is the action quickness, i.e. the effect onset has to show in relatively short times after consumption.

The nitroderivative compounds of formula (I), in the unmodified physical form according to the present invention, are known from the patent applications WO 95/30641 and WO 97/16405 in the name of the Applicant. These compounds with respect to the antiinflammatory precursor drugs have a global comparable or higher efficacy, but they have the advantage to show lower side effects. The drawback of these products is that they do not show chemical physical properties such as to allow an haematic peak of maximum absorption in the period of time of 2.5 hours at most. Pharmacokinetic studies carried out by the Applicant using a conventional pharmaceutical formulation for oral use of the nitroderivative compounds of formula (I), not treated as reported in the present invention, have shown that there is no haematic concentration peak in the above mentioned short times, therefore the product does not timely show its therapeutic

properties. See the Examples showing that the haematic peak takes place after too long times from the consumption, of about 6 hours.

The need was felt to have available pharmaceutical compositions for oral use, comprising the nitroderivative compounds of formula (I), such as to produce a maximum plasmatic concentration peak (C_{\max}) in short times, such that t_{\max} (t_{\max} being the time at which C_{\max} occurs) is of about 2.5 hours at most, preferably lower than or equal to 2 hours.

It has been found by the Applicant that it is possible to solve this technical problem with the compounds and formulations thereof for oral use as indicated hereinafter.

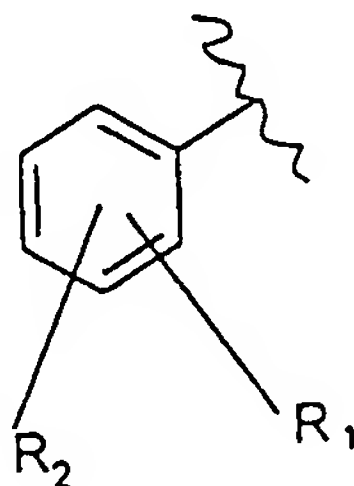
An object of the present invention are compounds of formula (I) and pharmaceutical compositions for oral use comprising as active principle said compounds



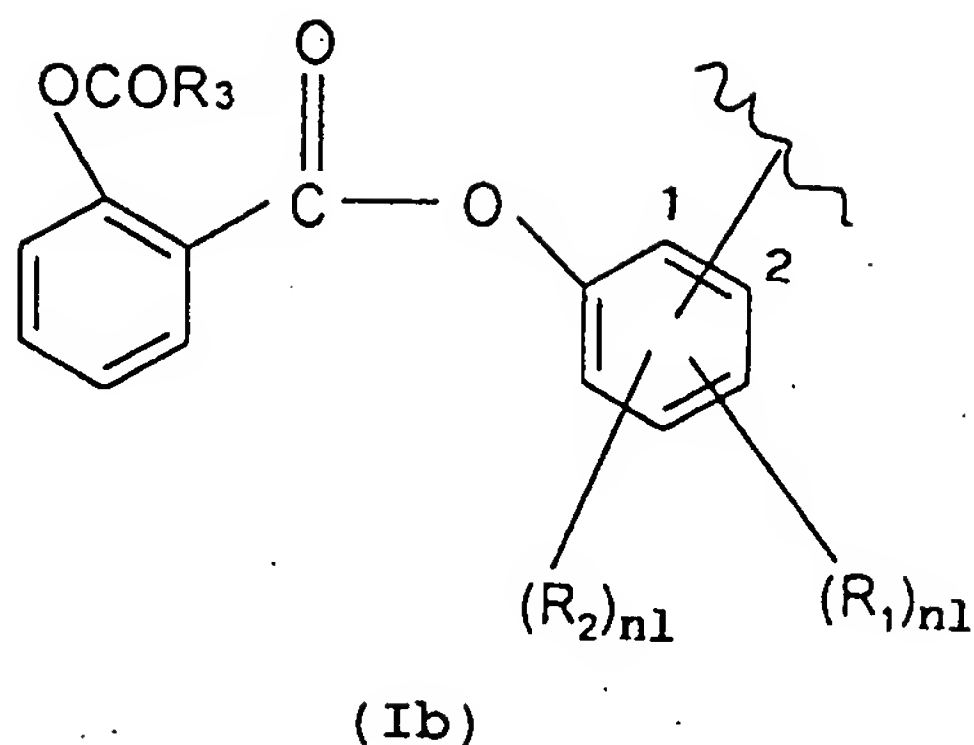
wherein

$A = R(COX_u)_t$, wherein t is 1, u is 1,

$X = O, NH, NR_{1C}$, wherein R_{1C} is a linear or branched C_1 - C_{10} alkyl, R is selected from the following radicals:



(Ia)



wherein:

R_1 is a $OCOR_3$ group; wherein R_3 is methyl, ethyl or linear or branched C_3 - C_5 alkyl, or the residue of a saturated heterocyclic ring having 5 or 6 atoms, which can be aromatic or completely or partially saturated, said heterocyclic ring containing one or more heteroatoms independently selected between O and N;

R_2 is hydrogen, hydroxy, halogen, linear or branched when possible C_1 - C_4 alkyl, linear or branched when possible C_1 - C_4 alkoxy; linear or branched when possible C_1 - C_4 perfluoroalkyl, for example trifluoromethyl; mono- or di- $(C_1$ - $C_4)$ alkylamino;

R_1 and R_2 together are the dioxymethylene group, with the proviso that when $X = NH$, then Y is ethylene and $R_2 = H$ as defined hereunder;

R_1 cannot be $OCOR_3$ in position 2 when R_3 is methyl;

nI is an integer and is 0 or 1.

Preferably in (Ia) $X = O$, R_1 is acetoxy and is in ortho position with respect to the $-CO-$ group, R_2 is hydrogen; preferably in Ib) $R_3 = CH_3$, $nI = 0$; X is equal to O, and the bond of the aromatic ring with the COX group is in the 1 or 2

positions;

X_1 is a bivalent linking bridge selected from the following:

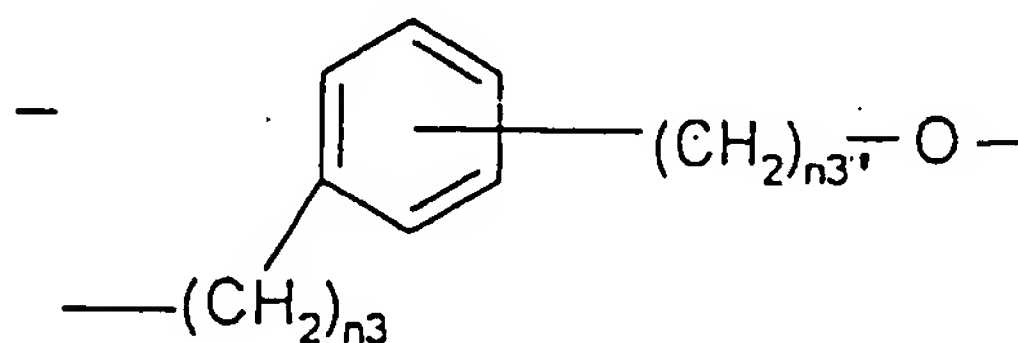
YO:

linear or branched when possible C_1-C_{20} , preferably

C_2-C_5 , alkylene; or

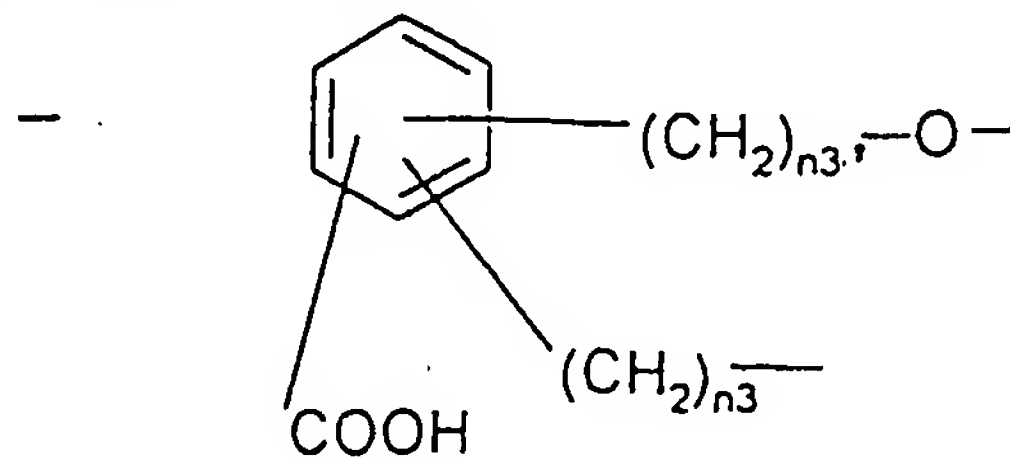
C_5-C_7 cycloalkylene optionally substituted;

or X_1 is selected from the following:



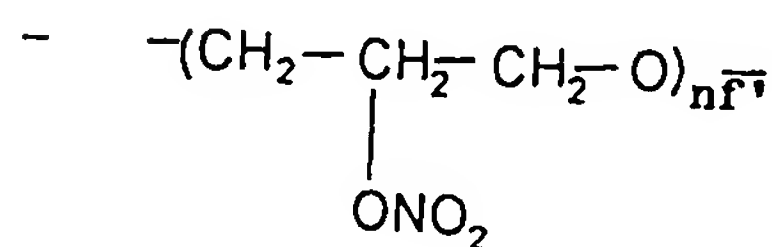
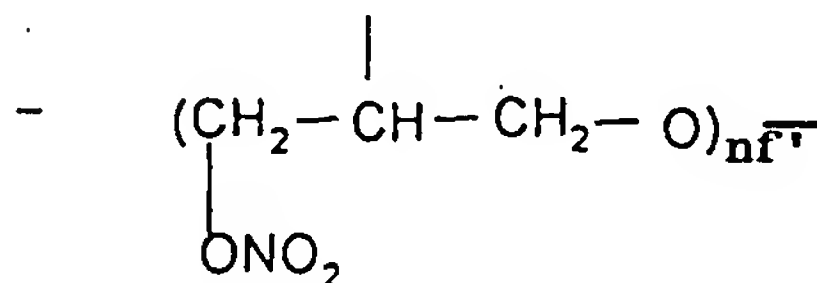
(PAI)

wherein $n3$ is an integer from 0 to 3, $n3'$ is an integer from 1 to 3;

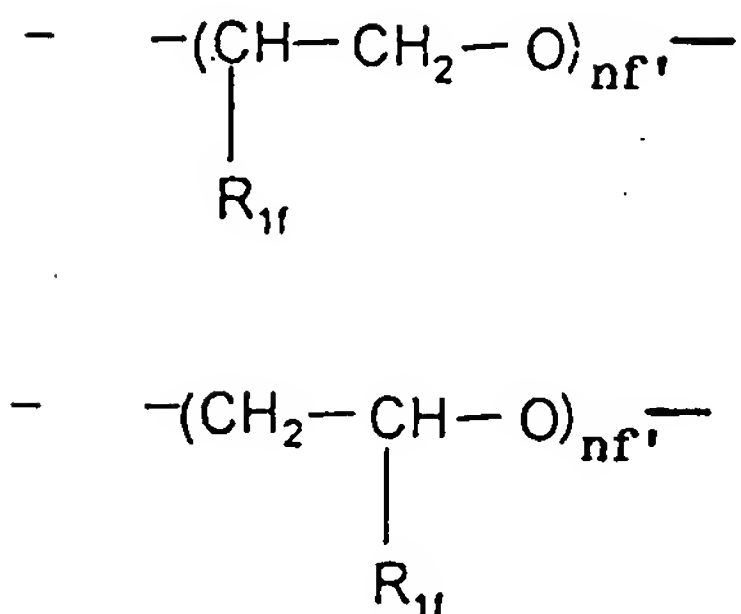


(PAII)

wherein $n3$ and $n3'$ have the above mentioned meaning;



wherein nf' is an integer from 1 to 6, preferably from 1 to 4;



wherein $R_{1f} = \text{H, CH}_3$ and nf' is as above defined;
 said compounds of formula (I) being completely or partially in amorphous form.

The amorphization degree can be measured by well known methods such as for example DSC, RX, IR, etc. For partially amorphous it is meant that in the pharmaceutical compositions of the invention the compounds of formula (I) are generally amorphous for at least 5%, preferably 10%, more preferably for at least 80%, as measured by DSC.

The amorphization degree is determined by DSC as variation (reduction) of the subtended area of the endothermic melting peak of the active principle. When the amorphization is complete, the melting peak characteristic of the active principle of formula (I) substantially disappears. This means that there is a variation of the enthalpy associated to the melting peak.

A test for measuring the amorphization degree according to the present invention is the following: an amount of nitroderivative of formula (I) is added with hydroxypropyl- β -

cyclodextrin in the molar ratio 1 : 2; 43 g of the compound of formula (I) are dissolved in 5 l of ethyl alcohol; the so obtained organic solution is mixed at room temperature with 5 l of deionized water containing 7% w/v (350 g) of hydroxypropyl- β -cyclodextrin. The hydroalcoholic solution is treated in the spray-drying LabPlant SD-05 Spray-Drying equipment, with an hot air flow at the inlet at the temperature of 60°C, maintaining an air flow such as to allow outlet temperatures of about 45°C; the crystallinity loss is evaluated on the powder (5-10 mg) by the DSC method and the variation of the peak area is determined by comparing the area with that of the precursor treated under the same conditions without the addition of cyclodextrin.

An indicative test of the crystallinity decrease of the compounds of formula (I) is based on the determination of their dissolution rate in water.

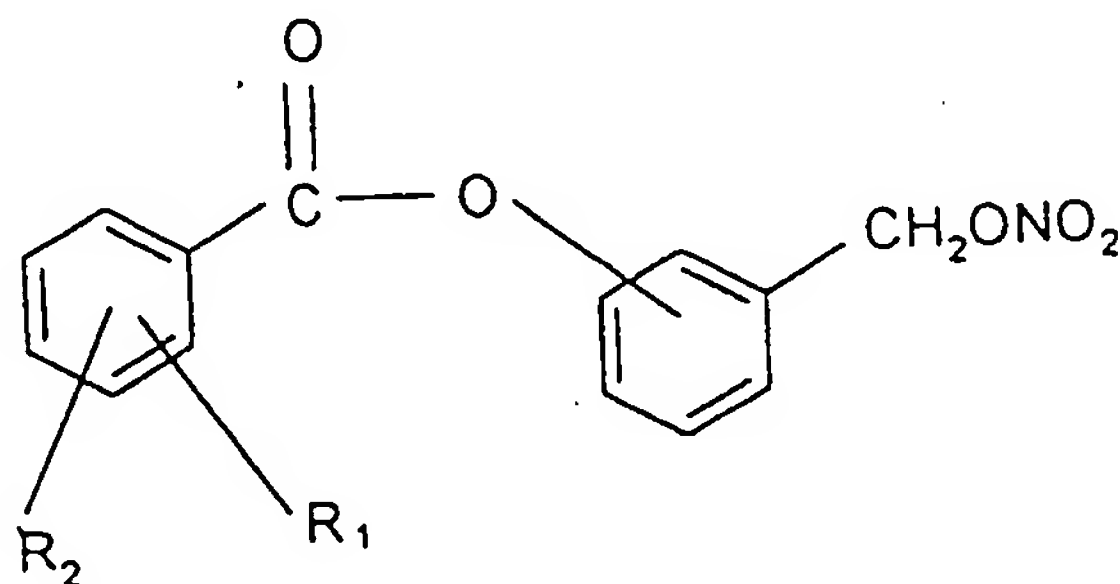
The dissolution rate test is carried out in a dissolving equipment according to United States Pharmacopeia 23 by using a volume of deionized water of 1000 ml. The blade stirrer speed is of 100 rpm and the temperature is $37 \pm 0.5^\circ\text{C}$.

In a little glass vessel an exact amount of each sample is weighed so that it contains an amount of the active principle equal to 30 mg, which is directly introduced in the vessel containing the deionized water. At predetermined times, respectively of 5, 10, 15, 30, 45, 50, 60, 90 and 120 minutes from the beginning of the test, the amount of the nitroderivative compound passed in solution is determined, by

measuring the concentration w/v (weigh/volume) thereof by UV spectrophotometry at the wave length of 235 nm, using a calibration line. The data are expressed as percentage of nitroderivative compound passed in solution in connection with the time. The amount of the compound of formula (I) passed in solution at the time of 10 minutes is at least about 10 times higher with respect to that of the nitroderivative compound not in amorphous form.

As said, the formulations of the invention are surprisingly and unexpectedly capable to induce in very short times, in the order of 2-2.5 hours, the plasmatic concentration peak of the hydroxybenzoic acid derivative A.

Preferably in the compounds of formula (I) $R = (Ia)$, $X = O$ and X_1 is the aromatic radical of formula (PAI) wherein $n_3' = 1$ and $n_3 = 0$; said preferred compounds having the following general formula (IA1):



(IA1)

wherein R_1 and R_2 are as above defined.

The ester of formula (IA1) wherein the nitroxymethyl group

is on the aromatic ring in meta position, or position 3, with respect to the carbon atom bound to the oxygen of the ester group, is preferred.

The Applicant has surprisingly and unexpectedly found that when the nitroderivatives of formula (I) are present in the pharmaceutical compositions of the invention in a completely or partially amorphized form, in consequence of gastrointestinal absorption, high plasmatic concentrations are obtained in very short times, the maximum plasmatic concentration peak is obtained in a period of time of 2.5 hours at most.

The partially or completely amorphized nitroderivative compounds of formula (I) are obtainable by treating the nitroderivatives with one or more excipients, capable to amorphize said nitroderivatives.

The techniques used for the amorphization are for example co-grinding, kneading, spray-drying, lyophilization, preferably spray-drying and co-grinding.

In particular in the spray-drying technique the active principle is dissolved in a solvent, for example alcohols, and the so obtained organic solution is mixed at room temperature with a solution or suspension of the excipient capable to give amorphization of the compounds of formula (I). The solution or suspension resulting after mixing is treated in a spray-drying equipment. For this and the other techniques see the specific Examples.

Excipients preferably belong to one or more classes men-

tioned hereinafter: C₅-C₆ polyalcohols, mono- and disaccharides and their derivatives, oligosaccharides containing from 3 to 10 saccharide units and their derivatives, polysaccharides, their derivatives including their salts, cyclodextrins and their derivatives, non cyclic cyclodextrin analogues, for example non cyclic derivatives of β -cyclodextrin, polymers and copolymers of vinyl-based monomeric units, and/or containing a carboxylic function, or (meth)acrylic monomers.

Examples of C₅-C₆ polyalcohols are sorbitol, mannitol; examples of monosaccharides and their derivatives are glucose, fructose, mannose, galactose glucosamine; example of disaccharides are lactose, saccharose, maltose etc; examples of polysaccharides and their derivatives are microcrystalline cellulose, hydroxypropylcellulose, hydroxyethylcellulose hydroxymethylcellulose, methylcellulose, ethylcellulose carboxymethylcellulose, and their salts, preferably sodium and calcium salts, and their crosslinked forms, cellulose acetate, cellulose acetophthalate and their ethers, for ex. cellulose phthalate hydroxypropylmethyl ether, starch and derivatives such as for example sodium carboxymethylstarch, soluble starch, pregelled starch; examples of cyclodextrins and derivatives thereof are dimethyl- β -cyclodextrin, 2-hydroxy-ethyl- β -cyclodextrin, 2-hydroxypropyl- β -cyclodextrin, 3-hydroxypropyl- β -cyclodextrin, trimethyl- β -cyclodextrin.

An object of the present invention are the pharmaceutical compositions for oral use containing as active principle the

partially or completely amorphized compounds of formula (I) and comprising at least one of the above mentioned excipients.

It has been found by the Applicant that the formulations of the invention show an improved dissolution rate in water, determined by the above described dissolution test.

In the compositions according to the present invention the ratio between the amount by weight of nitroderivatives of formula (I) and that of the excipients capable to amorphize the nitroderivatives is generally in the range 1 : 20 and 1 : 0.5, preferably 1 : 0.7 and 1 : 10.

As said, the formulations for oral use of the present invention are capable to induce in very short times, of the order of 2-2.5 hours, the plasmatic concentration peak of the hydroxybenzoic acid derivative as defined in A, and it has also been found that they are capable to produce the following pharmacokinetic effects:

to increase the plasmatic C_{MAX} (maximum concentration) of the hydroxybenzoic acid derivative as defined in A, after single administration, with respect to the untreated (not amorphized) product according to the present invention;

to increase of at least 20%, preferably of 50%, the area substended from the curve of the plasmatic concentrations in the range 0-3.5 hours from the administration.

When in the partially or completely amorphized product of formula (I) $R = (Ia)$ the hydroxybenzoic acid derivative as defined in A is the salicylic acid (see the Examples).

The nitroderivative compounds of formula (I) wherein R is a radical of formula Ia) or Ib) are obtainable according to the known methods in the prior art. See for example the methods described in the patent applications in the name of the Applicant WO 95/30641, WO 97/16405, or in the international patent application PCT/EP00/00353.

The following examples illustrate the invention without limiting the scope thereof.

EXAMPLES

A) Characterization of the compound of formula (I) by DSC

The characterization is exemplified for the 3-(nitroxymethyl)phenyl ester of the acetylsalicylic acid, the substance used in the examples described hereinafter, which has been obtained according to Example 1 of the international patent application PCT/EP00/00353.

The specific melting enthalpy ΔH (Joule/g) of the product as such and of the product treated with processes able to decrease the crystallinity (formulation) thereof, is determined by DSC analysis.

The per cent crystallinity loss is evaluated by the following equation:

$$\% \text{ crystallinity loss} = \frac{\Delta H_{\text{drug as such}} - \Delta H_{\text{treated drug}}}{\Delta H_{\text{drug as such}}} \times 100$$

The scanning parameters adopted for the DSC analysis are

the following:

Scanning range: from 30°C min. to 330°C max

Scanning rate: 10K/min

The DSC trace of the ester as such shows a melting endothermic peak at $T = 64.7^{\circ}\text{C}$ with respective $\Delta H = 99,81$ Joule/g.

B) Dissolution rate test of the compound of formula (I) 3-(nitroxymethyl)phenyl ester of the acetylsalicylic acid

The dissolution rate of 3-(nitroxymethyl)phenyl ester of the acetylsalicylic acid as such and in the preparations containing it according to the examples described hereinafter, has been carried out in a dissolving equipment according to USP (United States Pharmacopeia) XXIII.

The test is carried out by using a volume of deionized water of 1000 ml. The angle rate of the blade stirrer is of 100 rpm and the temperature of $37 \pm 0.5^{\circ}\text{C}$.

In a little glass vessel an exact amount of each preparation to be tested is weighed so that it contains an amount of the active principle equal to 30 mg, which is directly introduced in the vessel. At predetermined times, respectively of 5, 10, 15, 30, 45, 50, 60, 90 and 120 minutes from the beginning of the test the amount of the compound passed in solution is determined, by measuring the concentration w/v thereof by UV spectrophotometry at the wave length of 235 nm, using a calibration line. The data are expressed as percentage of active principle passed in solution in connection with the time.

EXAMPLE 1 (comparative)

Dissolution rate of 3-(nitroxymethyl)phenyl ester of the completely crystalline acetylsalicylic acid

The recrystallized product from isopropanol results completely crystalline, and by DSC analysis it shows an endothermic peak at $T = 64.7^{\circ}\text{C}$ with ΔH 99.81 J/g, and an exothermic decomposition peak at $T = 220^{\circ}\text{C}$ with ΔH 879.47 J/g.

30 mg of said compound are transferred into the equipment for determining the dissolution rate. In Table 1 the percentages of the compound passed in solution, measured at the times indicated in the above described test, are reported. After 10 minutes the amount of active principle passed in solution is 0.3%.

EXAMPLE 2

Obtainment of 3-(nitroxymethyl)phenyl ester of the completely amorphous acetylsalicylic acid by spray-drying treatment of the compound in admixture with hydroxypropyl- β -cyclodextrin in the ratio by weight compound : cyclodextrin 1 : 8.33 corresponding to a molar ratio of 1 : 2.

43 g of the compound are dissolved in 5 l of ethyl alcohol. The so obtained organic solution is mixed at room temperature with 5 l of deionized water containing 7% w/v (350 g) of hydroxypropyl- β -cyclodextrin. The hydroalcoholic solution is treated in the spray-drying LabPlant SD-05 Spray-Drying equipment, with a hot air flow at the inlet at the temperature of 60°C , maintaining an air flow such as to allow outlet temperatures of

about 45°C.

The compound crystallinity loss, measured on the so obtained powder according to the DSC method is of 100%. In fact in the DSC trace the melting endothermic peak is absent.

An amount of the powder corresponding to 30 mg of active principle is weighed and transferred into the equipment for determining the dissolution rate. In Table 1 the percentages of the compound passed in solution, measured at the times indicated in the above described dissolution test, with respect to the weighed amount, are reported. After 10 minutes the active principle % passed in solution is 32%.

EXAMPLE 3

Obtainment of 3-(nitroxymethyl)phenyl ester of the partially amorphous acetylsalicylic acid by spray-drying treatment of the compound in admixture with lactose in the ratio 1 (compound) : 9 (lactose) by weight.

10 g of the compound are dissolved in 1.5 l of ethyl alcohol. The obtained organic solution is mixed with 1.5 l of deionized water containing 6% w/v (90 g) of lactose. The hydroalcoholic solution is treated in the spray-drying equipment, operating with an hot air flow at the inlet of 70°C, maintaining an air flow such as to allow outlet temperatures of about 50°C.

The crystallinity loss, measured according to the DSC method on the so obtained powder is of 87% (ΔH 12.58 J/g).

An amount of powder equal to 30 mg of active principle is weighed and transferred into the equipment for determining the

dissolution rate. In Table 1 the percentages of the compound passed in solution, measured at the times indicated in the above described dissolution test, are reported. After 10 minutes the % of active principle passed in solution is 30%.

EXAMPLE 3A

Obtainment of 3-(nitroxymethyl)phenyl ester of the partially amorphous acetylsalicylic acid by the spray-drying treatment of the compound in admixture with microcrystalline cellulose in the 1 : 0.7 ratio.

10 g of the compound are dissolved in 1.5 l of ethyl alcohol. To the solution 0.670 litres of a 1% w/v (weight/volume) aqueous suspension of microcrystalline cellulose (Avicel PH 101) are added. The suspension is submitted to spray-drying, operating with an air temperature at the inlet of 70°C and maintaining an air flow such as to allow outlet temperatures of about 50°C.

An amount of powder equal to 30 mg of active principle is weighed and transferred into the equipment for determining the dissolution rate. In Table 1 the percentages of the compound passed in solution, measured at the times indicated in the above described dissolution test, are reported. After 10 minutes the % of active principle passed in solution is of 9.4%. The crystallinity loss is 10%.

EXAMPLE 3B

Obtainment of 3-(nitroxymethyl)phenyl ester of the partially amorphous acetylsalicylic acid by treatment by co-milling in

admixture with microcrystalline cellulose and sodium lauryl sulphate in ratios by weight active principle : microcrystalline cellulose : surfactant equal to 1 : 0.5 : 0.1.

10 g of the active principle are mixed in a mortar with 1 g of sodium lauryl sulphate for 5 minutes and subsequently with 5 g of microcrystalline cellulose. The powder mixture is forcedly co-milled with a pestle for 30 minutes.

The dissolution test is carried out by using 48 mg of the obtained mixture, equal to 30 mg of the active principle.

The percentages of the compound passed in solution, at the times indicated in the above described dissolution test, are reported in Table 1. The % of active principle passed in solution after 10 minutes is equal to 4.8%.

The powder DSC analysis shows a crystallinity loss of the active principle of 6%.

EXAMPLE 4

Obtainment of 3-(nitroxymethyl)phenyl ester of the partially crystalline acetylsalicylic acid by spray-drying treatment of the compound in admixture with lactose in the ratio 1 (compound) : 4 (lactose) by weight.

10 g of the compound are dissolved in 1.5 l of ethyl alcohol. The obtained organic solution is mixed with 0.75 l of deionized water containing 6% w/v (45 g) of lactose. The hydroalcoholic solution is treated in the spray-drying equipment, operating with an hot air flow at the inlet of 70°C, maintaining an air flow such as to allow outlet temperatures of about 50°C.

The crystallinity loss, evaluated on the so obtained powder according to the DSC method, is of 83% (ΔH 16.44 J/g).

An amount of the obtained powder corresponding to 30 mg of active principle is weighed and transferred into the equipment for determining the dissolution rate. The percentages of the compound passed in solution, at the times mentioned in the dissolution test indicated in B), are reported in Table 1. After 10 minutes the active principle % passed in solution is of 17.1%.

EXAMPLE 5

Obtainment of 3-(nitroxymethyl)phenyl ester of the partially amorphous acetylsalicylic acid by co-milling treatment of the compound in admixture with hydroxypropyl- β -cyclodextrin in the ratio compound : cyclodextrin of 1: 4.16 by weight corresponding to a molar ratio 1 : 1.

10 g of the compound are mixed with 41.6 g of cyclodextrin. The mixture is co-milled in a mortar for 30 minutes.

The crystallinity loss, evaluated on the so obtained powder according to the DSC method, is of 43% (ΔH 56.5 J/g).

An amount of the obtained powder corresponding to 30 mg of active principle is weighed and transferred into the equipment for determining the dissolution rate. The percentages of the compound passed in solution, at the times mentioned in the dissolution test indicated in B), are reported in Table 1. After 10 minutes the active principle % passed in solution is of 6.9%.

EXAMPLE 6

Obtainment of 3-(nitroxymethyl)phenyl ester of the partially amorphized acetylsalicylic acid by treating the compound by kneading in admixture with lactose in the ratio 1 compound : 9 lactose by weight.

5 g of the compound are directly mixed with 45 g of lactose. The mixture is kneaded with 10 ml of ethanol 50% in water and then let dry under vacuum of the water pump at room temperature for 24 hours. The dried product is sieved by a sieve with 600 μ m meshes before the analyses.

The crystallinity loss, measured on the so obtained powder according to the DSC method, is of 7% (ΔH 92.34 J/g).

An amount of the obtained powder corresponding to 30 mg of active principle is weighed and transferred into the equipment for determining the dissolution rate. The percentages of the compound passed in solution, at the times mentioned in the dissolution test indicated in B), are reported in Table 1. After 10 minutes the % of active principle passed in solution is of 11.5%.

EXAMPLE 6A

Example 6 was repeated but using a mixture comprising also hydroxypropyl- β -cyclodextrin, in ratios active principle : lactose : hydroxypropyl- β -cyclodextrin 1 : 0.5 : 0.2 by weight.

1000 g of the active principle are mixed with 500 g of lactose and 200 g of hydroxypropyl- β -cyclodextrin. The mixture is kneaded by a mechanical kneader with 100 ml of a solution 3% w/v of polyvinylpyrrolidone in water/isopropyl alcohol 1 : 1,

operating by progressive additions.

The kneading is extruded through a granulator die, and dried in a drier at the temperature of 40°C. The dried granulate is passed through the mesh of an oscillating granulator, in order to uniform the granulometry.

An amount of the obtained powder corresponding to 30 mg of active principle is weighed and transferred into the equipment for determining the dissolution rate. The percentages of the compound passed in solution, at the times indicated in the dissolution test described in B), are reported in Table 1. After 10 minutes the % of active principle passed in solution is of 15.6%. The crystallinity loss is of 39.4%.

EXAMPLE 7 (comparative)

Spray-drying of the active principle as such

16 g of 3-(nitroxymethyl)phenyl ester of the acetylsalicylic acid are dissolved in 3 l of a mixture of ethyl alcohol/water 80/20. The hydroalcoholic solution is treated in the spray-drying equipment with an hot air flow at the inlet of 60°C, maintaining an air flow such as to allow outlet temperatures of about 45°C.

The DSC analysis on the obtained powder shows that the compound is in a completely crystalline form (ΔH 100.5 J/g).

30 mg of powder of the active principle is weighed and transferred into the equipment for determining the dissolution rate. The percentages of the compound passed in solution, measured at the times indicated in the dissolution test de-

scribed in A), are reported in Table 1. After 10 minutes the % of active principle passed in solution is of 0.5%, therefore not substantially different from that obtained in the dissolution test of the active principle as such (ref. Example 1).

EXAMPLE 8 (comparative)

Preparation of tablets according to the prior art containing: 300 mg of 3-(nitroxymethyl)phenyl ester of the acetylsalicylic acid, 143.7 mg of microcrystalline cellulose, 3 mg of talc, 3 mg of magnesium stearate and 0.3 mg of silica

300 g of active principle are mixed in a mortar with 0.3 g of colloidal silica, 143.7 g of microcrystalline cellulose added in aliquots, according to the subsequent dilution method. Then 3 g of talc are added. The mixture is transferred into a powder mixer (Turbula) and mixed for 10 minutes. 3 g of magnesium stearate are added and mixing is continued for further 5 minutes. The powder mixture is directly compressed by a rotative compressor (Officine Ronchi) equipped with bombed punches (9.5 mm diameter; 9 mm bending radius) obtaining tablets having an average weight of 450 mg and an average strenght at break of 10 kg. The so obtained tablets are crumbled in a mortar until obtaining a powder capable to pass the 200 μ m meshes of a sieve. An amount of the obtained powder corresponding to 30 mg of active principle is weighed and transferred into the equipment for determining the dissolution rate. The percentages of the compound passed in solution, at the times indicated in the dissolution test described in B), are reported in Table 1.

After 10 minutes the active principle % passed in solution is of 0.34%.

The DSC analysis does not show any evidence of the active principle amorphization due to compacting.

TESTS IN VIVO

EXAMPLE 9

Pharmacokinetic in the animal by using the pharmaceutical composition according to the present invention described in Example 3B.

A single dose of 80 mg/Kg, equal to 50 mg/Kg of active principle, of the pharmaceutical composition (powder) of Example 3B in aqueous suspension (5 ml/Kg) was administered by os to a group of 10 rats weighing 180-200 g.

Samples of 0.5 ml of blood were taken from the caudal vein of the animals after 0.5, 1, 1.5, 2, 4, 8, 12 and 24 hours from administration.

The samples are transferred into heparinised test tubes and centrifuged for 15 minutes at room temperature. A 100 µl aliquot of serum was added with 25 µl of an internal standard solution (prepared by dissolving 10 mg of naproxene in 100 ml of acetonitrile). The sample is injected in a HPLC Hewlett Packard series 1050 equipment, having a variable wave length detector, pump, self-sampler with a 5 µm ODS 2 (10X 0.46 cm) column connected in series to a 5 µm ODS 2 (C18-250X 4 mm) column. The moving phase is constituted by acetonitrile/acetic acid 3% in the ratio 60/40 by volume. The flow is 0.8 ml/min. All the

analyses have been carried out at room temperature and the measures have been effected at the wave length of 234 nm. The C_{Max} value is 61.7 $\mu\text{g/ml}$ at the time of 2 hours.

EXAMPLE 10 (comparative)

Pharmacokinetic in the animal by using the pharmaceutical composition described in Example 8.

A single dose of 75 mg/Kg, equal to 50 mg/Kg of active principle, of the powder obtained from the crumbled tablets described in Example 8 in aqueous suspension (5 ml/Kg) was administered by os to a group of 10 rats weighing 180-200 g.

Samples of 0.5 ml of blood were taken from the caudal vein of the animals after 1.5, 3, 6, 12 and 24 hours from administration. One proceeds as described in the previous Example 8. The C_{Max} value is 53.2 $\mu\text{g/ml}$ at the time of 6 hours.

Table 1

Dissolution test on the samples of the active principle of the Examples												
Time (minutes)	% by weight of the active principle passed in solution											
	Ex. 1 Comp.	Ex. 2	Ex. 3	Ex. 3A	Ex. 3B	Ex. 4	Ex. 5	Ex. 6	Ex. 6A	Ex 7 Comp.	Ex. 8 comp.	
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
5	0.1	29.9	28.7	5.1	2.7	14.2	3.8	6.9	10.8	0.3	0.2	
10	0.3	32.4	29.3	9.4	4.8	17.1	6.9	11.5	15.6	0.5	0.3	
15	0.4	33.0	29.2	12.3	6.4	18.7	9.0	14.3	18.1	0.8	0.5	
30	0.8	32.5	28.1	16.4	9.3	20.2	11.8	18.1	21.3	1.5	0.9	
45	1.2	32.5	27.6	19.1	11.4	21.6	13.9	20.7	23.0	2.2	1.4	
60	1.6	32.3	27.2	20.9	12.9	22.6	15.6	22.5	23.9	2.7	1.9	
90	2.4	31.9	26.4	22.4	15.0	23.6	17.6	24.0	24.8	4.0	2.7	
120	3.1	31.7	26.3	23.5	16.6	24.5	19.4	25.1	25.6	5.2	3.7	

CLAIMS

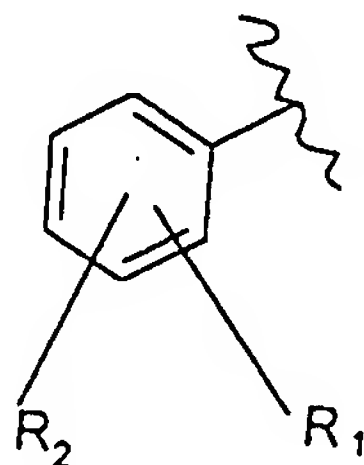
1. Compounds of formula (I)



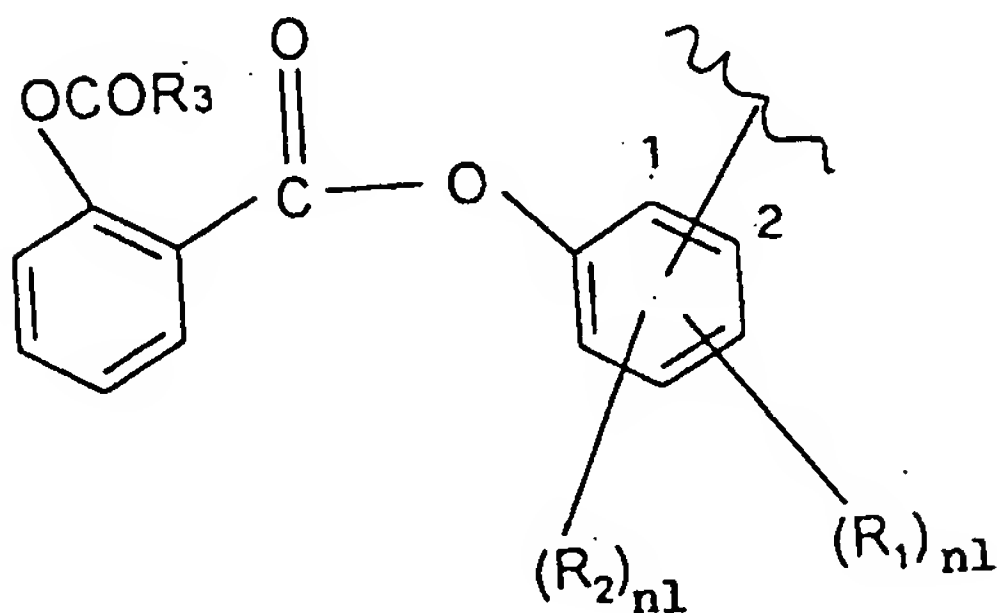
wherein

$A = R(COX_u)_t$, wherein t is 1, u is 1,

$X = O, NH, NR_{1C}$, wherein R_{1C} is a linear or branched C_1 - C_{10} alkyl, R is selected from the following radicals:



(Ia)



(Ib)

wherein:

R_1 is a $OCOR_3$ group; wherein R_3 is methyl, ethyl or a linear or branched C_3 - C_5 alkyl, or the residue of a saturated heterocyclic ring having 5 or 6 atoms, which can be aromatic or completely or partially saturated, said heterocyclic ring containing one or more heteroatoms independently selected from O and N and S;

R_2 is hydrogen, hydroxy, halogen, linear or branched when possible C_1 - C_4 alkyl, linear or branched when possible C_1 - C_4 alkoxy; linear or branched when possible C_1 - C_4 perfluoroalkyl, for example trifluoromethyl; mono- or di- (C_1 - C_4) alkylamino;

R_1 and R_2 together are the dioxymethylene group, with the proviso that when $X = NH$, then Y is ethylene and $R_2 = H$ as defined hereunder;

R_1 cannot be $OCOR_3$ in position 2 when R_3 is methyl;

nI is an integer and is 0 or 1;

preferably in (I) $X = O$, R_1 is acetoxy and it is in ortho position with respect to the $-CO-$ group, R_2 is hydrogen;

preferably in Ib) $R_3 = CH_3$, $nI = 0$; X is equal to O , and the aromatic ring bond with the COX group is in the 1 or 2 positions;

X_1 is a bivalent linking bridge selected from the following:

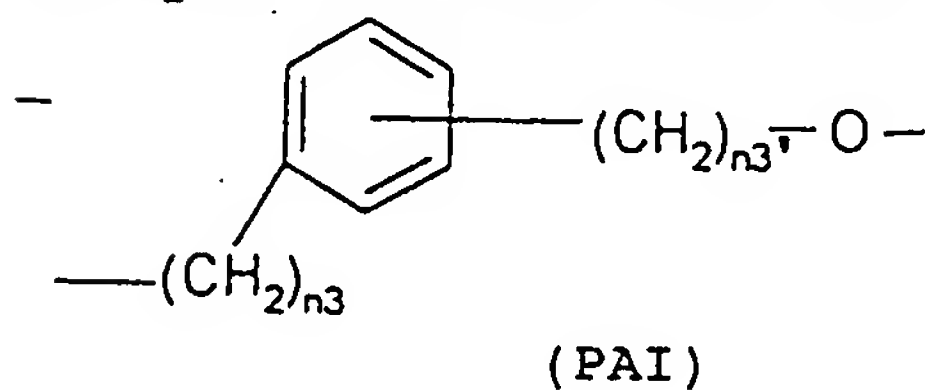
YO:

linear or branched when possible C_1 - C_{20} , preferably

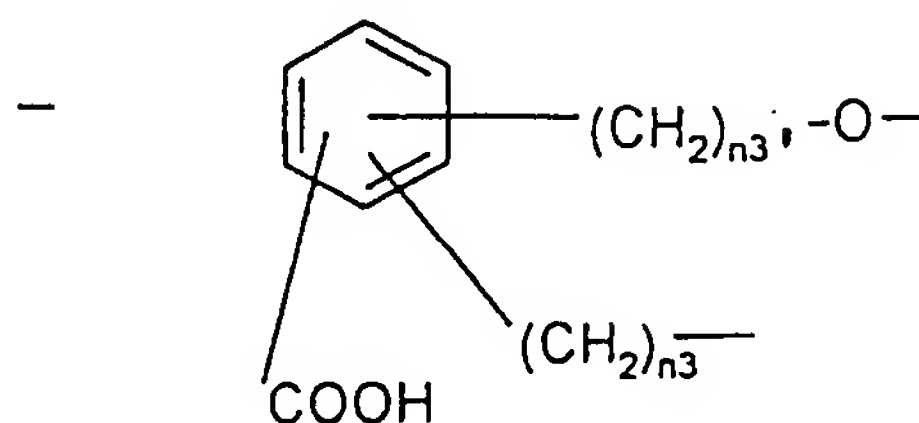
C_2 - C_5 , alkylene; or

C_5 - C_7 cycloalkylene optionally substituted;

or X_1 is selected from the following:

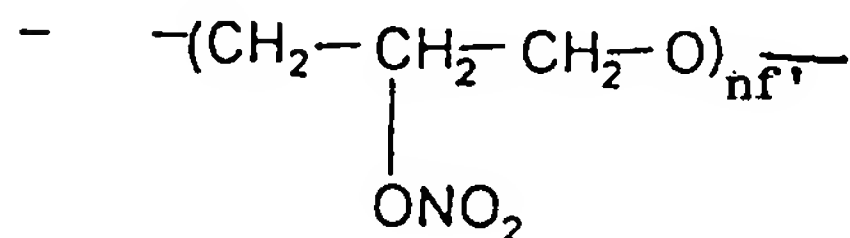
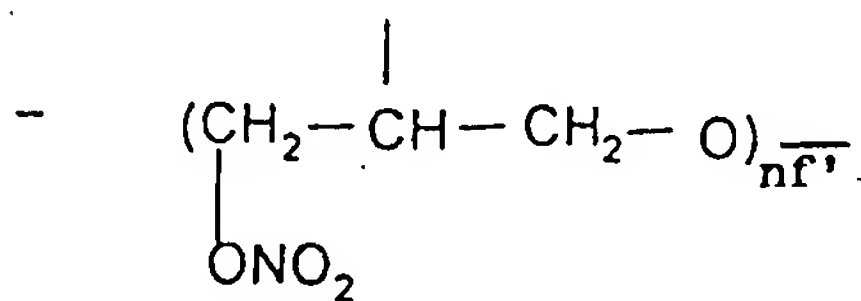


wherein n_3 is an integer from 0 to 3, n_3' is an integer from 1 to 3;

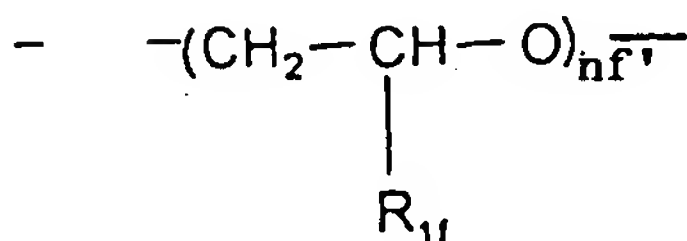
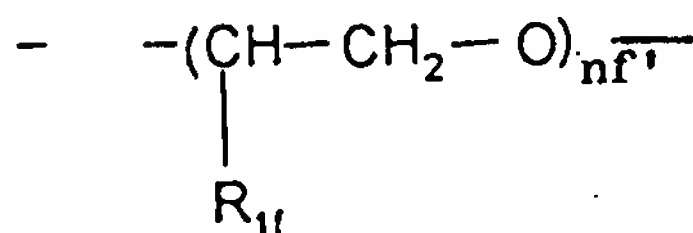


(PAII)

wherein n_3 and n_3' have the above mentioned meaning;



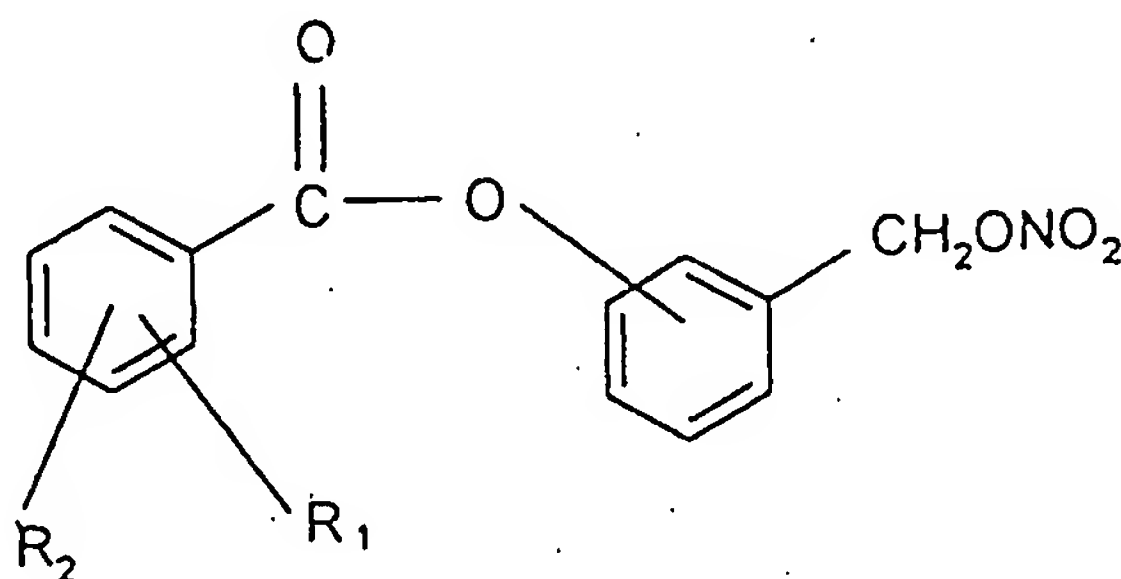
wherein nf' is an integer from 1 to 6, preferably from 1 to 4;



wherein $R_{1f} = \text{H}, \text{CH}_3$ and nf' is as above defined;

said compounds of formula (I) being completely or partially amorphous.

2. Compounds according to claim 1 amorphous for at least 5%, preferably 10%, more preferably for at least 80%, amorphization being measured by DSC.
3. Compounds according to claims 1 and 2, wherein in the formula (I) $R = (Ia)$.
4. Compounds according to claim 3, wherein in formula (I) $R = (Ia)$, $X = O$ and X_1 is the aromatic radical of formula (PAI) wherein $n_{3'} = 1$ and $n_3 = 0$; said preferred compounds having the following general formula (IA1):



(IA1)

wherein R_1 and R_2 are as above defined.

5. Compounds according to claims 1-4 obtainable by formulating nitroderivatives with one or more excipients, capable to amorphize nitroderivatives.
6. Compounds according to claim 5, wherein the excipients belong to one or more classes mentioned hereinafter: C_5 - C_6 polyalcohols, mono- and disaccharides and their derivatives, oligosaccharides containing from 3 to 10 saccharide units and their derivatives, polysaccharides, their

derivatives including salts, cyclodextrins and their derivatives, non cyclic cyclodextrin analogues, for example non cyclic derivatives of β -cyclodextrin, polymers and copolymers of vinyl-based monomeric units, and/or containing a carboxylic function, or (meth)acrylic monomers.

7. Compounds according to claims 5-6, wherein the ratio between the amount by weight of nitroderivatives of formula (I) and that of the excipients is in the range 1 : 20 and 1 : 0.5, preferably 1 : 0.7 and 1 : 10.
8. A process for preparing the compounds of claims 1-7, wherein amorphization is obtained by using co-grinding, kneading, spray-drying, lyophilization.
9. A process according to claim 8, wherein the method used for amorphization is co-grinding.
10. Pharmaceutical compositions comprising the compounds of claims 1-7.
11. Pharmaceutical compositions according to claim 10 for oral use.
12. Compounds according to claims 1-7 for use as a medicament.
13. Use of the compounds according to claim 12 as anti-inflammatory drugs.

INTERNATIONAL SEARCH REPORT

Intern. Application No.
PCT/EP 00/05723

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C203/04 A61K31/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 621 000 A (DEL SOLDATO PIERO ET AL) 15 April 1997 (1997-04-15) example 1 claims	1-13
A	US 5 597 847 A (MATJI JOSE A ET AL) 28 January 1997 (1997-01-28) examples claims	1-13
A	WO 98 57967 A (CHA BONG JIN ;KIM SU EON (KR); OH JUN GYO (KR); DONG A PHARMACEUTI) 23 December 1998 (1998-12-23) abstract page 1, line 16 - line 20 page 3, line 17 -page 4, line 16 claims 1-3	1-13



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

21 September 2000

Date of mailing of the international search report

02/10/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

O'Sullivan, P

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 00/05723

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



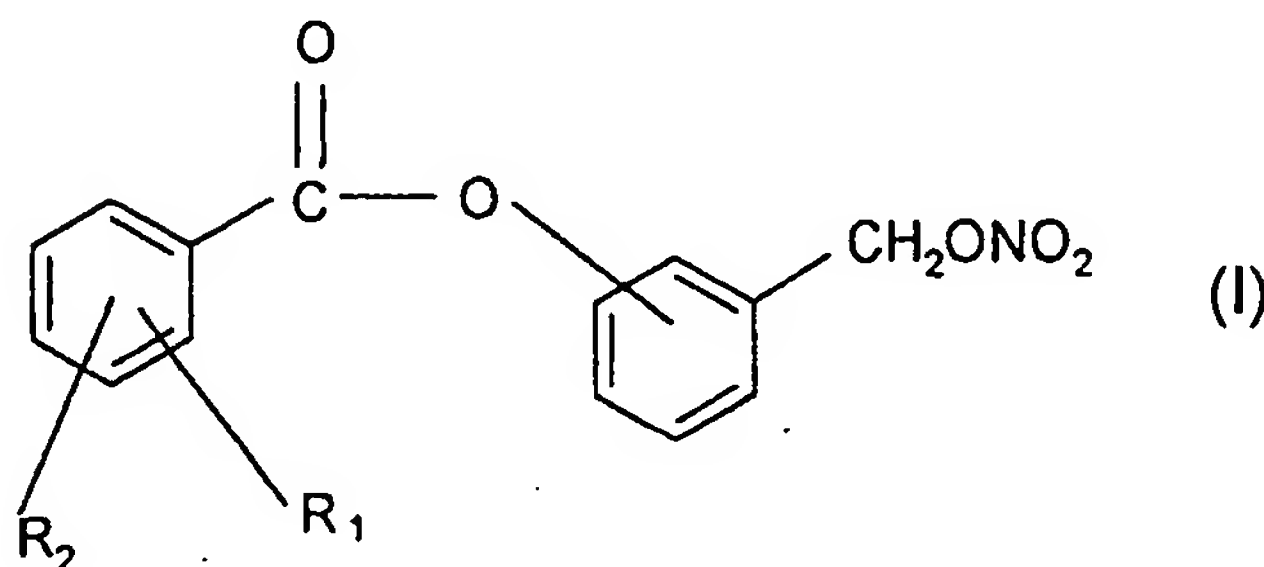
(43) International Publication Date
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number
WO 01/04082 A1

- (51) International Patent Classification⁷: C07C 203/04, 201/02, 67/14, 69/90
- (74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni, 2, I-20129 Milano (IT).
- (21) International Application Number: PCT/EP00/05722
- (81) Designated States (*national*): AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA.
- (22) International Filing Date: 21 June 2000 (21.06.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
MI99A001517 9 July 1999 (09.07.1999) IT
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): NICOX S.A. [FR/FR]; 45, avenue Kléber, F-75116 Paris (FR).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): CASTALDI, Graziano [IT/IT]; Via Livia Gallina, 5, I-28072 Briona (IT). OLDANI, Erminio [IT/IT]; Via San Massimo, 82, I-20018 Sedriano (IT). RAZZETTI, Gabriele [IT/IT]; Via G. Puccini, 60, I-20099 Sesto S. Giovanni (IT). BENEDINI, Francesca [IT/IT]; Via Padova, 286, I-20100 Milano (IT).
- Published:
- With international search report.
 - Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: A PROCESS FOR OBTAINING (NITROXYMETHYL)PHENYL ESTERS OF SALICYLIC ACID DERIVATIVES



(57) Abstract: A process for obtaining (nitroxymethyl)phenyl esters of salicylic acid derivatives of formula (I) wherein R₁ is the OCOR₂ group characterized in that it comprises the following steps: a) reaction of a halide of a salicylic acid derivative with hydroxybenzylalcohol in the presence of a base; b) nitration of the obtained product in anhydrous conditions by a mixture of nitric acid with a different inorganic acid, or an organic acid, or an anhydride of one or two organic acids; c) recovery of the final product.

WO 01/04082 A1

A PROCESS FOR OBTAINING (NITROXYMETHYL)PHENYL ESTERS OF SALICYLIC ACID DERIVATIVES.

* * * *

The present invention relates to a process for obtaining (nitroxymethyl)phenyl esters of salicylic acid derivatives.

It is known in the prior art that the (nitroxymethyl)phenyl esters of the salicylic acid derivatives can be prepared by various synthesis processes. In the patent application WO 97/16405 the reaction of the acyl chloride of the acetylsalicylic acid with (nitroxymethyl)phenol is described. The (nitroxymethyl) phenol is prepared by a synthesis which comprises the following steps:

- reaction of the phenol with HBr in organic solvent to obtain (bromomethyl)phenol, and
- reaction of the (bromomethyl) phenol in organic solvent with AgNO₃ with formation of (nitroxymethyl)phenol.

The process based on the reaction between (nitroxymethyl) phenol and the acyl chloride of the acetylsalicylic acid shows the following drawbacks:

- the (bromomethyl)phenol obtained in the first synthesis step is a chemically unstable and irritating compound;
- the nitrating agent used in the reaction with (bromomethyl)phenol is a very expensive reactant;
- the (nitroxymethyl)phenol is an unstable compound, which can easily decompose in an uncontrollable way; and it must be purified before the reaction with the acetylsalicylic acid chloride, furtherly increasing the production costs and requiring supplementary units in the production plant.

In conclusion the synthesis of above derivatives, by using the intermediate (nitroxymethyl) phenol, is difficult and expensive to be carried out on an industrial scale.

In PCT Patent EP 00/00353 in the name of the Applicant a

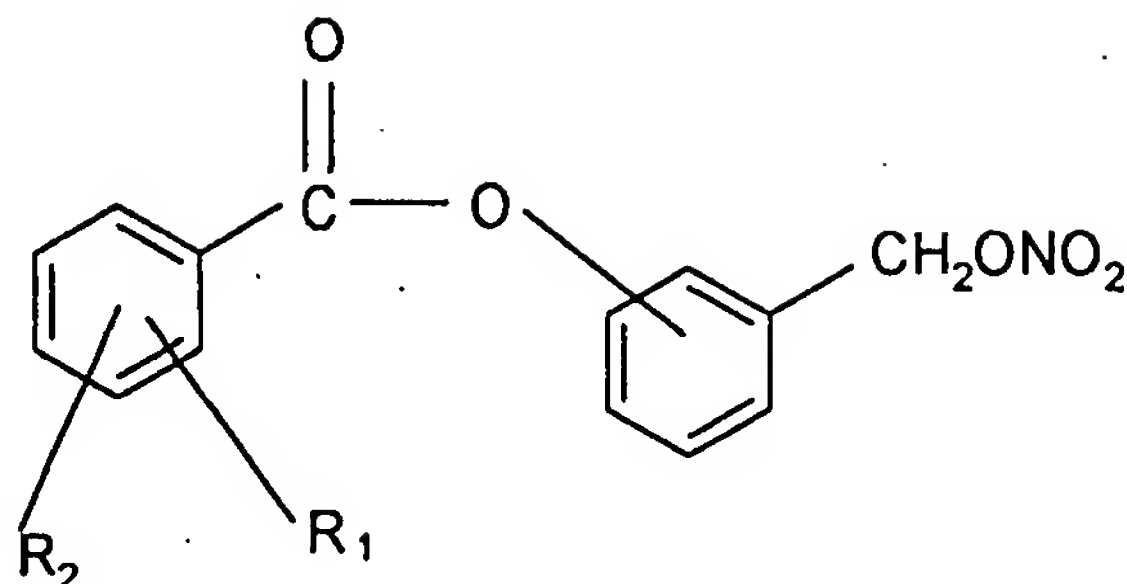
synthesis process of nitroxy derivatives of formula (I) (see hereunder) is described, by submitting to nitration with AgNO_3 (hydroxymethyl) phenyl esters of the acetylsalicylic acid, obtained by reacting the acid chloride with hydroxybenzaldehyde and reducing the aldehydic group to primary alcohol. Also this process, as the above mentioned uses silver nitrate as nitrating agent and therefore it is not much advantageous from an industrial point of view. Besides the process global yields are not high.

By using the teaching of the prior art, it is possible to obtain the salicylic acid nitroxyderivatives of formula (I) (see below) by reacting a (hydroxymethyl)phenyl ester of the acetylsalicylic acid with nitrating reactants based on nitric acid. However under the reaction conditions of the prior art the nitric acid produces undesired reactions, such as for example the nitration of aromatic substrata (ref. "Nitration: Methods and Mechanism", 1984 VCH ed., p. 269) and the oxidation of primary alcohols to aldehydes (ref. "Industrial and Laboratory Nitration" 1976 ACS publ., p. 156).

Therefore also said processes of the prior art are unable to solve the problem of the preparation on industrial scale of the nitroxyderivatives of the salicylic acid as above defined.

The need was felt to prepare nitroxy derivatives of (hydroxymethyl)phenyl esters of the acetylsalicylic acid by a process cheaper than those of the prior art both for the nitrating agent used and for the yields, and substantially without the drawbacks of the prior art.

An object of the present invention is a process for obtaining (nitroxymethyl)phenyl esters of the salicylic acid derivatives, compounds having the following formula (I):



(I)

wherein:

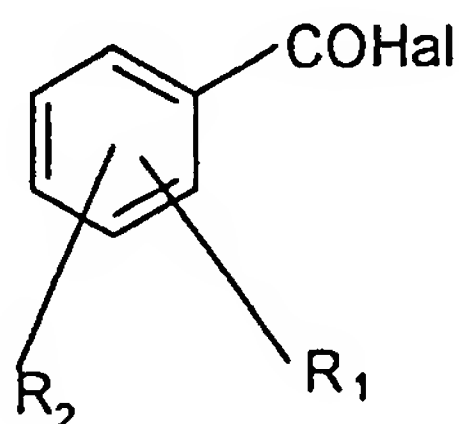
R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or linear or branched C_3 - C_5 alkyl, or the residue of a saturated heterocyclic ring having 5 or 6 atoms, containing hetero-atoms independently selected between O and N;

R_2 is hydrogen, halogen, linear or branched when possible C_1 - C_4 alkyl, linear or branched when possible C_1 - C_4 alkoxy; linear or branched when possible C_1 - C_4 perfluoroalkyl, for example trifluoromethyl; mono- or di- (C_1 - C_4)alkylamino;

preferably in (I) R_1 is acetoxy and is in ortho position with respect to the carboxylic group, R_2 is hydrogen; the oxygen of the ester group is bound to the aromatic ring substituted with the (nitroxy)methylene group in ortho, meta or para position with respect to the (nitroxy)methylene group; preferably the position is the meta one;

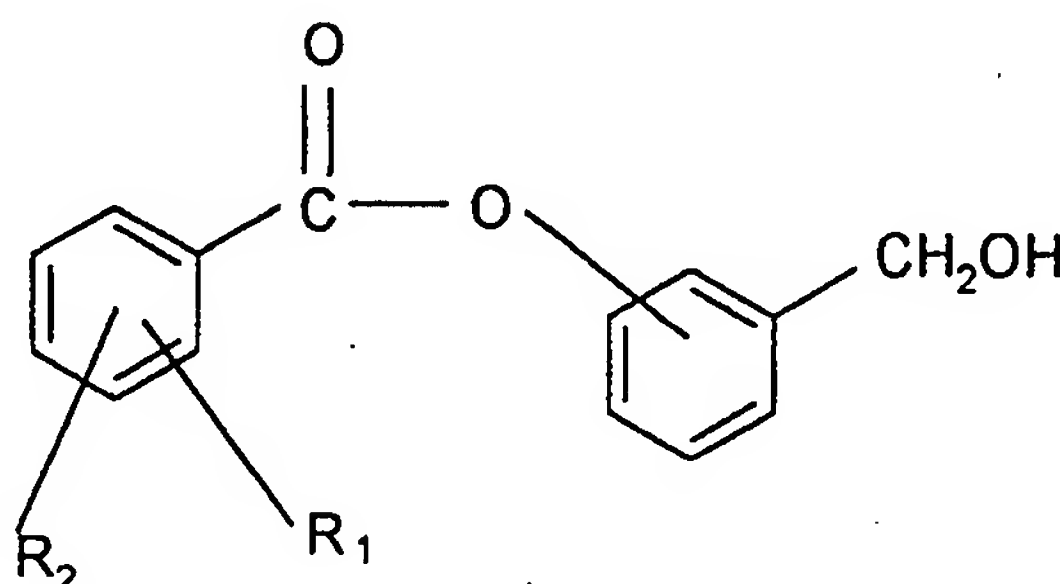
said process comprising the following steps:

- a) reaction of a halide of a salicylic acid derivative of formula (I-A):



(I-A)

wherein Hal = Cl, Br, and R₁ and R₂ have the above indicated meaning, with hydroxybenzylalcohol in the presence of a base, in an organic solvent, or in a mixture of water with a miscible or immiscible organic solvent with water, to give the compound (I-B) having the following formula:



(I-B)

wherein R₁ and R₂ are as above defined;

- b) nitration of the compound (I-B) in anhydrous conditions, in an inert organic solvent, by a mixture formed by steaming nitric acid with an inorganic acid different from nitric acid or with an organic acid, or with the anhydride of one or two organic acids, to give the nitroxyderivative of formula (I).
- c) recovery of the final product by adding water to the organic phase, separating the phases, drying and evaporating the organic phase.

In step a) the base can be an inorganic base, such as for example hydroxides, oxides, carbonates and bicarbonates of alkaline metals (sodium, potassium, lithium); or an organic base, for example a tertiary amine, for example aliphatic, cycloaliphatic, heterocyclic, heterocyclic aromatic, such as triethylamine, diisopropyl-ethylamine, N-methylmorpholine, diazaabicyclooctane, etc.

The organic solvent used in step a) can be an organic solvent miscible with water such as C₁-C₄ aliphatic alcohols, for example methanol, ethanol, isopropanol, n-butanol; or an

organic solvent immiscible with water for example aromatic hydrocarbons such as toluene and xylene, chlorinated organic solvents such as methylene chloride, chlorobenzene, other solvents which can be used are aliphatic esters for example of C_1 - C_4 acids with C_1 - C_5 alcohols such as for example ethyl acetate and butyl acetate, etc.: aliphatic and cycloaliphatic ketones, such as C_3 - C_{12} , for example acetone, methylketone, cyclohexanone, etc.

In step a) the reaction is carried out at a temperature in the range -20°C and $+50^{\circ}\text{C}$, preferably 0°C - 20°C , by using, with respect to the hydroxybenzylalcohol moles under reaction, an amount by moles of acid halide (I-A) in a ratio between 1 and 2, preferably between 1.2 and 1.5, and an amount by moles of base between 0.1 and 2, preferably between 1 and 2.

The compound I-B) is recovered from the reaction mixture by addition of water and optionally, when the reaction takes place in an aqueous solvent or in a mixture of water with an hydrosoluble organic solvent, by addition of an organic solvent immiscible with water, such as ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried, evaporated and the product is recovered. If necessary, the compound can be purified by crystallization from solvents such as for example n-hexane, n-heptane, ligroin, toluene, methanol, isopropanol, diisopropylether, etc or their mixtures. Generally the yields are higher than 80%.

In step b) the nitration reaction is carried out at a temperature in the range -20°C and $+40^{\circ}\text{C}$, preferably from 0°C to 20°C ; the used amount by moles of nitric acid is in a ratio between 1 and 6, preferably 1 and 3, with respect to the moles of the hydroxyester (I-B); the amount by moles of organic or inorganic acid different from nitric acid, or of anhydride as above defined, is in a ratio comprised between 0.5 and 6, preferably between 1 and 3 with respect to the moles of the compound (I-B).

The inorganic acid different from nitric acid is for example sulphuric acid; the organic acid is for example methansulphonic acid, trifluoromethansulphonic acid, trifluoroacetic acid, trichloroacetic acid, acetic acid; the organic

acid anhydride is for example acetic anhydride, trifluoromethanesulphonic anhydride, trifluoroacetic anhydride, trichloroacetic anhydride, etc., or mixed anhydrides such as for example trifluoroacetic-trifluoromethanesulphonic anhydride, etc.

The inert organic solvent used in step b) is a solvent which has boiling point lower than 200°C at atmospheric pressure and it can be a chlorinated solvent, such as for example dichloromethane; or a nitroalkane such as for example nitromethane, or an aliphatic or cycloaliphatic ether such as for example methylterbutylether, tetrahydrofuran, etc.; an ester for example ethyl acetate; or an aliphatic or aromatic nitrile such as for example acetonitrile, benzonitrile.

The solvent volume is not critical, generally the volume is comprised between 1 and 20 times with respect to the amount by weight of hydroxyester (I-B) under reaction.

When the nitration in step b) is carried out in the presence of an organic anhydride as above defined, preferably the anhydride is first mixed with the hydroxyester (I-B) and then the resulting mixture is added to the nitric acid solution in the inert organic solvent.

Preferably the used organic anhydride is acetic anhydride.

In step c) it is possible to recrystallize the obtained compound by using solvents such as for example n-hexane, n-heptane, ligroin, methanol, isopropanol or their mixtures.

The following Examples describe the invention without limiting the scope thereof.

EXAMPLE 1a

Preparation of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (compound I-B) in admixture water-organic solvent

3-hydroxymethylphenol (25.25 g, 0.2 moles) is dissolved in a 5% hydroxide sodium solution (160 ml). To the so obtained solution an acetylsalicylic acid chloride solution (40.4 g, 0.2 moles) in dichloromethane (50 ml) is added at room temperature, under stirring. The mixture is maintained at room temperature under stirring for 2 hours and then extracted with dichloromethane (2 x 100 ml). The organic phase is separated,

anhydrified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from a mixture of ethyl acetate and hexane. 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (45.8 g, 0.16 moles, yield 80%) is obtained.

M.P.: 79°-81°C.

¹H NMR(CDCl₃) δ (ppm): 2.29 (s, 3H); 4.71 (s, 2H); 7.07-8.2 (m, aromatics, 8H).

EXAMPLE 1b

Preparation of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (compound I-B) in organic solvent immiscible with water

3-hydroxymethylphenol (10 g, 0.08 moles) is dissolved in toluene (50 ml) containing triethylamine (9.8 g, 0.1 moles). To the so obtained solution an acetylsalicylic acid chloride solution (16 g, 0.08 moles) in toluene (50 ml) is added at a temperature of 5°-10°C under stirring. The mixture is maintained at a temperature in the above mentioned range, under stirring for 2 hours, then poured in water and then extracted with dichloromethane (2 x 100 ml). The organic phase is separated, washed in sequence with a 25% w/v potassium carbonate solution, with water, with a 3% hydrochloric acid solution and lastly with water again, then anhydrified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol. 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (45.8 g, 0.16 moles, yield 80%) is obtained.

M.P.: 79°-81°C.

¹H NMR(CDCl₃) δ (ppm): 2.29 (s, 3H); 4.71 (s, 2H); 7.07-8.2 (m, aromatics, 8H).

EXAMPLE 1c

Preparation of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (compound I-B) in organic solvent miscible with water

3-hydroxymethylphenol (10 g, 0.08 moles) is dissolved in acetone (50 ml). In the obtained solution potassium carbonate in powder (22.2 g, 0.16 moles) is suspended. To the suspension

an acetylsalicylic acid chloride solution (16 g, 0.08 moles) in acetone (50 ml) is added at a temperature of 5°-10°C, under stirring. The mixture is maintained at a temperature in the above mentioned range, under stirring, for 2 hours, then filtered and the solvent evaporated under vacuum. The residue is crystallized from isopropanol. 3-hydroxymethylphenyl ester of the 2-acetoxy-benzoic acid (21.0 g, 0.07 moles, yield 91%) is obtained.

M.P.: 79°-81°C.

¹H NMR(CDCl₃) δ (ppm): 2.29 (s, 3H); 4.71 (s, 2H); 7.07-8.2 (m, aromatics, 8H).

EXAMPLE 2

Preparation of 3-nitroxymethylphenyl ester of the 2-acetoxy-benzoic acid by nitration with steaming nitric acid, in the presence of sulphuric acid, of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid.

A solution of steaming nitric acid (3.92 g, 62.2 mmol, 3 moles with respect to the moles of the hydroxyester I-B) and sulphuric acid 96% (6.10 g, 62.2 mmol, 3 moles with respect to the moles of the hydroxyester I-B) in dichloromethane (25 ml) is cooled at 0°C and added in 1 hour, under stirring and in nitrogen atmosphere, with a 3-hydroxymethylphenyl ester solution of the 2-acetoxybenzoic acid (6 g, 20.7 mmol) in 25 ml of dichloromethane. The mixture is then diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydriified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol obtaining the 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (5.6 g, 17 mmol, yield 82%).

M.P.: 61°-62°C.

¹H NMR(CDCl₃) δ (ppm): 2.31 (s, 3H); 5.44 (s, 2H); 7.16-8.22 (m, aromatics, 8H).

EXAMPLES 2a-2f

Example 2 was repeated by varying the moles of nitric acid and of sulphuric acid with respect to the moles of the intermediate 3-hydroxymethylphenyl ester of the 2-

acetoxybenzoic acid (I-B). In the following Table 1 the molar ratios of the used reactants with respect to the compound I-B and the relative per cent ratio between the 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (I), the 3-(formyl)phenyl ester of the 2-acetoxybenzoic acid (I-B1) are reported, considering, when present, also the starting compound (I-B).

The Table shows that the highest yield is obtained by using the molar ratio nitric acid/compound (I-B) equal to 3 and sulphuric acid/compound (I-B) equal to 1.5.

Table 1

Example	Moles HNO ₃ /I-B	Eq. H ₂ SO ₄ /I-B	Moles H ₂ SO ₄ /I-B	Relative Ratio %		
				(I)	(I-B)	(I-B1)
a	2	0	0	5	15	80
b	2	1	0.5	25	0	75
c	1	1	0.5	54	0	46
d	1	0.5	0.25	5	14	55
e	2	2	1	69	0	31
f	3	3	1.5	99	0	1

EXAMPLE 3

Preparation of 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid by nitration with steaming nitric acid, in the

presence of acetic anhydride, of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid.

A solution of steaming nitric acid (1.44 g, 22.8 mmol), acetic anhydride, (2.33 g, 22.8 mmol) in dichloromethane (25 ml) is cooled at 0°C and under stirring added in 1 hour, in nitrogen atmosphere, with a 3-hydroxymethylphenyl ester solution of the 2-acetoxybenzoic acid (6 g, 20.7 mmol) in 25 ml of dichloromethane. The mixture is heated up to 20°C in one hour and then diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydriified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol and 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (5.6 g, 17 mmol, yield 82%) is obtained.

EXAMPLE 4

Preparation of 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid by nitration with steaming nitric acid, in the presence of acetic anhydride, of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (acetic anhydride mixed with hydroxyester).

A solution of steaming nitric acid (1.44 g, 22.8 mmol), in dichloromethane (25 ml) is cooled at 0°C and added in 1 hour, under stirring and in nitrogen atmosphere, with a solution of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (6 g, 20.7 mmol) and acetic anhydride (2.33 g, 22.8 mmol) in 25 ml of dichloromethane. The mixture is heated up to 20°C in one hour and then diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydriified with sodium shulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol to give 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (6.42 g, 19.5 mmol, yield 94%).

EXAMPLE 5

Preparation of 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid by nitration with steaming nitric acid, in the presence of methansulphonic acid, of 3-hydroxymethylphenyl

ester of the 2-acetoxybenzoic acid.

A steaming nitric acid solution (1.44 g, 22.8 mmol) and methanesulphonic acid (2.55 g, 22.8 mmol) in dichloromethane (25 ml) is cooled at 0°C and under stirring added in 1 hour, in nitrogen atmosphere, with a 3-hydroxymethylphenyl ester solution of the 2-acetoxybenzoic acid (6 g, 20.7 mmol) in 25 ml of dichloromethane. The mixture is diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydriified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol to give 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (2.73 g, 8.29 mmol, yield 40%).

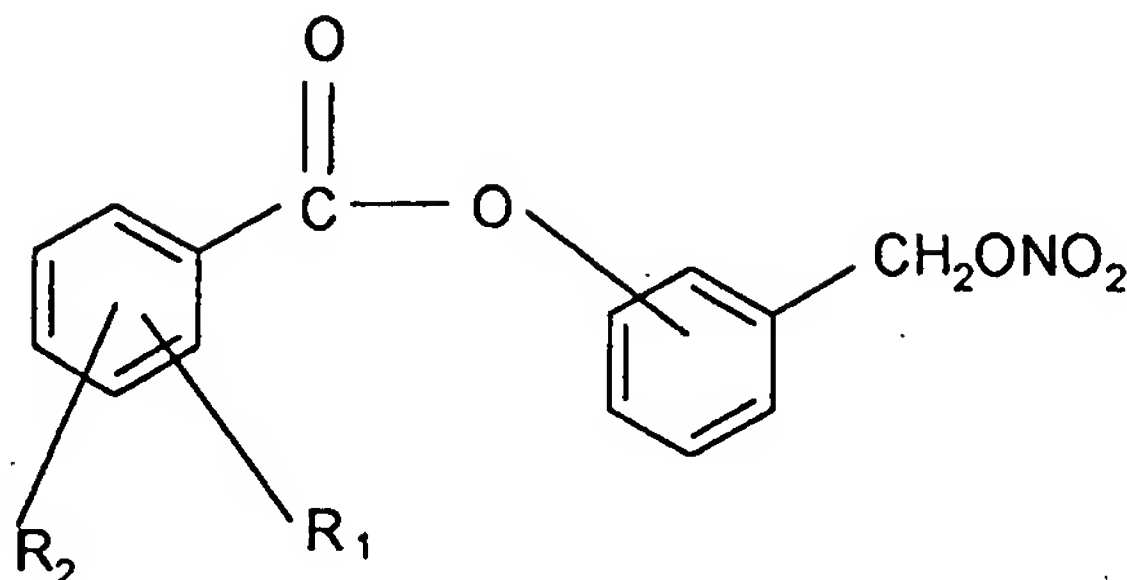
EXAMPLE 6

Preparation of 3-nitroxymethylphenyl ester of 2-acetoxybenzoic acid by nitration with steaming nitric acid, in the presence of acetic anhydride, of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid.

A steaming nitric acid solution (990 mg, 15.2 mmol), acetic anhydride (1.55 g, 15.2 mmol) in dichloromethane (25 ml) is cooled at 0°C and, under stirring, added in 1 hour, under nitrogen atmosphere, with a solution of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (4 g, 13.8 mmol) in 25 ml of dichloromethane. The mixture is heated in one hour up to 20°C and then diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydriified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol to give 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (4.1 g, 12.28 mmol, yield 89%).

CLAIMS

1. A process for obtaining compounds of formula (I):



(I)

wherein:

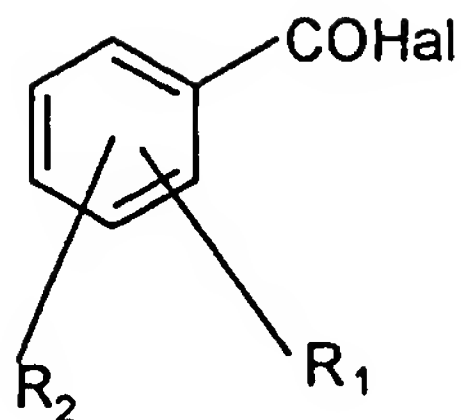
R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or linear or branched C_3 - C_5 alkyl or the residue of a saturated heterocyclic ring having 5 or 6 atoms, containing heteroatoms independently selected between O and N;

R_2 is hydrogen, halogen, linear or branched when possible C_1 - C_4 alkyl, linear or branched when possible C_1 - C_4 alkoxy; linear or branched when possible C_1 - C_4 perfluoroalkyl; mono- or di- (C_1 - C_4) alkylamino;

preferably in (I) R_1 is acetoxy and it is in ortho position with respect to the carboxylic group, R_2 is hydrogen; the oxygen of the ester group is bound to the aromatic ring substituted with the (nitroxy)methylene group in ortho, meta or para position with respect to the (nitroxy)methylene group; preferably the position is the meta one;

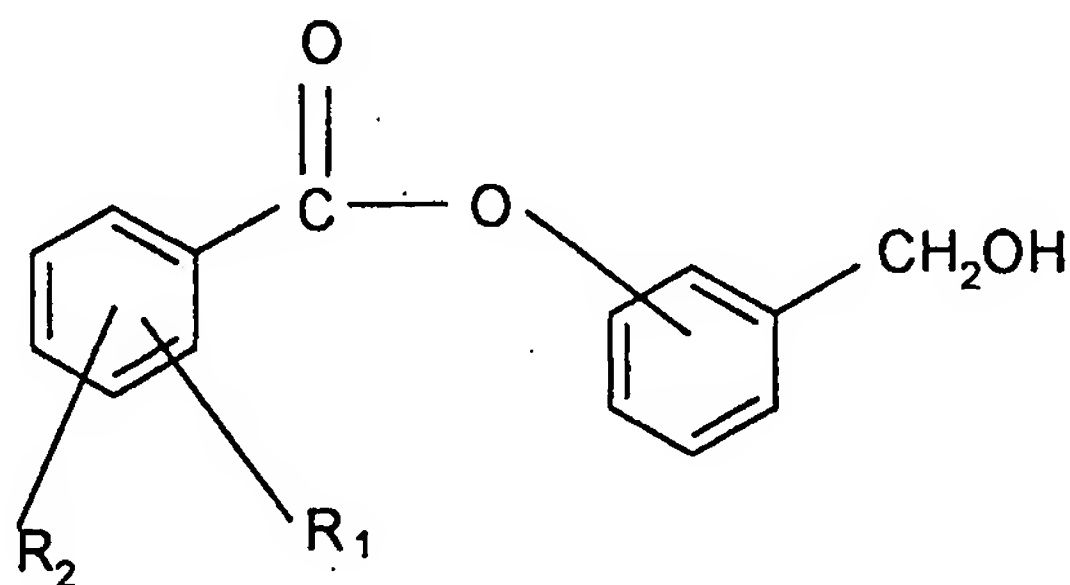
said process comprising the following steps:

- a) reaction between an halide of a salicylic acid derivative of formula (I-A)



(I-A)

wherein Hal = Cl, Br, and R₁ and R₂ have the above indicated meaning, with hydroxybenzylalcohol in the presence of a base in an organic solvent, or in a mixture of water with an organic solvent miscible or immiscible with water, to give the compound (I-B) having the following formula:



(I-B)

wherein R₁ and R₂ are as above defined;

- b) nitration of the compound (I-B) in anhydrous conditions, in an inert organic solvent, by a mixture formed by steaming nitric acid with an inorganic acid different from nitric acid, or with an organic acid, or with an anhydride of one or two organic acids to give the nitroxy derivative of formula (I).
- c) recovery of the final product by adding water to the organic phase, separating the phases, drying and

evaporating the organic phase.

2. A process according to claim 1, wherein in step a) the base is an inorganic or organic base.
3. A process according to claims 1-2, wherein in step a) the organic solvents are C₁-C₄ aliphatic alcohols; aromatic hydrocarbons, aliphatic esters, chlorinated organic solvents, aliphatic and cycloaliphatic ketones.
4. A process according to claims from 1 to 3, wherein in step a) the reaction is carried out at a temperature in the range -20°C and +50°C by using, with respect to the hydroxybenzylalcohol moles under reaction, an amount by moles respectively of acid halide (I-A) in the range between 1 and 2, preferably between 1.2 and 1.5 and an amount by moles of base in the range between 0.1 and 2, preferably between 0.5 and 2.
5. A process according to claim 1, wherein in step b) nitration is carried out at a temperature in the range -20°C and +40°C and the amount by moles of nitric acid is in a ratio between 1 and 6, preferably between 1 and 3, with respect to the moles of the compound (I-B), the amount by moles of inorganic acid different from nitric acid, or of organic acid or of organic anhydride as above defined, is in a ratio comprised between 0.5 and 6, preferably between 1 and 3 with respect to the moles of the compound (I-B).
6. A process according to claim 5, wherein nitration is carried out in the presence of an anhydride, which is premixed with the hydroxyester (I-B) and the resulting mixture added to the nitric acid solution in the inert organic solvent.
7. A process according to claim 6, wherein anhydride is acetic anhydride.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/05722

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C203/04 C07C201/02 C07C67/14 C07C69/90

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 16405 A (NICOX SA) 9 May 1997 (1997-05-09) cited in the application page 14 -page 15	1-4
A	WO 92 01668 A (ITALFARMACO SPA) 6 February 1992 (1992-02-06) page 5, line 19 - line 29; claim 1	1
A	WO 95 09831 A (NICOX LTD) 13 April 1995 (1995-04-13) claims 15,16	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

9 November 2000

Date of mailing of the international search report

22/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bonnevalle, E

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/EP 00/05722

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information on patent family members

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PCT/EP 00/05722

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number
WO 01/10814 A1

- (51) International Patent Classification⁷: C07C 203/04 (74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni, 2, I-20129 Milano (IT).
- (21) International Application Number: PCT/EP00/07222
- (22) International Filing Date: 27 July 2000 (27.07.2000) (81) Designated States (*national*): AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA.
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
MI99A001753 4 August 1999 (04.08.1999) IT (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): NICOX S.A. [FR/FR]; 45, avenue Kléber, F-75116 Paris (FR).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): BENEDINI, Francesca [IT/IT]; Via Padova, 286, I-20100 Milano (IT). OLDANI, Erminio [IT/IT]; Via San Massimo, 82, I-20018 Sedriano (IT). CASTALDI, Graziano [IT/IT]; Via Livia Gallina, 5, I-28072 Briona (IT). TARQUINI, Antonio [IT/IT]; Via Postumia, 23/2, I-15057 Tortona (IT).
- Published:
— With international search report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 01/10814 A1

(54) Title: PROCESS FOR THE PREPARATION OF NAPROXENE NITROXYALKYLESTERS

(57) Abstract: A process for obtaining nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid having an enantiomeric excess higher than or equal to 95 %, preferably higher than or equal to 98 %, characterized in that an halide of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula A-Hal, wherein A is the acid acyl residue, is reacted in an inert organic solvent with an aliphatic nitroxyalkanol HO-Y-ONO₂, wherein Y is a C₂-C₂₀ alkylene or a cycloalkylene from 3 to 8 carbon atoms, or an alkylene as defined containing a cycloalkylene as defined, in the presence of an inorganic base.

PROCESS FOR THE PREPARATION OF NAPROXENE NITROXYALKYLESTERS

* * * * *

The present invention relates to a new method for preparing nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (naproxene) having an enantiomeric excess of the (S) form higher than or equal to 97%, preferably higher than or equal to 98%, combined with high yields, higher than 75-80%, preferably higher than 85%.

It is well known in the prior art that the enantiomeric form (S) is the active form from the pharmacological point of view of the above mentioned product.

In the prior art synthesis methods of nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid, are known. In the patent application WO 98/25,918, a synthesis method of naproxene nitroxyalkyl esters containing in the alkyl chain a saturated C₃-C₈ cycloalkyl residue, is described. In said process the acid or one of its functional derivatives, for example, chloride or anhydride, is reacted, in an inert organic solvent, with a nitroalkanol containing a cycloalkyl residue as above defined. The reaction takes place in the presence of an organic nitrogenated base, such as for example 4-dimethyl aminopyridine, morpholine, N-methyl morpholine or triethylamine. Tests carried out by the Applicant have shown

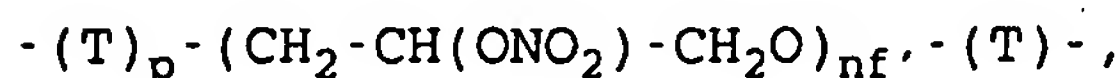
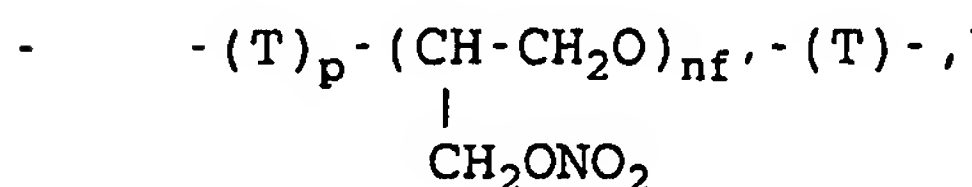
that this process of the prior art does not allow to obtain naproxene nitroxyalkylesters having an enantiomeric excess in the range of 55-80%, only with a specific organic base, 4-N,N-dimethylamino pyridine, 94% is obtained.

The need was therefore felt to obtain naproxene nitroxyalkylesters having an higher enantiomeric excess, at least of 97%, preferably equal to or higher than 98%.

An object of the present invention is a process to obtain nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid having an enantiomeric excess higher than or equal to 97%, preferably higher than or equal to 98%, characterized in that an halide of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula A-Hal, wherein A is the acyclic residue of said acid, is reacted in an inert organic solvent with an aliphatic nitroxyalkanol HO-Y-ONO₂, wherein Y has one of the following meanings:

- a linear or optionally branched C₁-C₂₀, preferably C₂-C₅, alkylene;
- a cycloalkylene with ring from 3 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, said cycloalkylene optionally can be substituted with one or two alkylenes as above defined, and/or with one or more alkyl radicals having in the chain a number of carbon atoms as above defined for alkylene;
- an aromatic residue with ring having 5 or 6 carbon atoms,

said aromatic residue optionally can be substituted with one or two alkylenes as above defined, and/or with one or more alkyl radicals having in the chain a number of carbon atoms as above defined for alkylene, or a -COOH group;



T being alkylene as above defined and p an integer equal to zero or one, alkylene having the above mentioned meaning, nf' is an integer from 1 to 6, preferably from 1 to 4; in the presence of an inorganic base, to give the corresponding nitroxyalkylester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula A-O-Y-ONO₂, wherein A and Y are as above defined.

Y can also be a combination of two or more of the mentioned group.

The aliphatic nitroxyalcohol amount on molar basis is in the range 1-2, preferably 1.2-1.5, with respect to that of the acid halide.

With inorganic bases hydroxides, oxides, carbonates and bicarbonates, silicates, aluminosilicates of the alkaline and alkaline-earth metals, or hydroxides, oxides, carbonates and bicarbonates of metals belonging to the group IIB, preferably zinc, or to groups IIIa or IVa, preferably tin, are meant.

The inorganic base amount is in molar ratio with the acid

halide amount generally in the range 1-2, preferably 1.2-1.5.

With inert organic solvent according to the present invention aromatic hydrocarbons are meant, such as for example toluene and xylene, chlorinated or fluorinated organic solvents, for example methylene chloride, chlorobenzene, aliphatic esters for example C_1 - C_4 acids esters with C_1 - C_5 alcohols such as for example ethyl acetate and butyl acetate, etc.

The solvent amount is not critical and generally from 1 to 10 volumes of solvent are used, preferably from 2 to 5 volumes based on the acid halide weight.

The reaction is carried out at a temperature in the range -20°C and 50°C , preferably 0°C and 20°C .

The nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid are recovered at the end of the reaction, after addition of water to the organic phase, separation of the phases and solvent evaporation. If necessary, a further purification can be carried out by chromatography on silica gel column in order to increase the product titre.

Alternatively, the compound can also be purified by crystallization from a suitable solvent.

Aliphatic nitroxyalcohols can be prepared according to the known methods in the prior art. See for example Gazzetta Chim. It. 1987, 117, 173 and WO 98/25,918.

The Applicant has found that surprisingly by the use of

inorganic bases it is possible to improve the enantiomeric excess of naproxene nitroxyalkylesters with respect to the prior art methods, which use, as seen, organic bases, with high yields as above mentioned.

The following examples have the purpose to illustrate the invention and they are not to be intended as limitative thereof.

EXAMPLE 1 (comparative)

Preparation of 4-nitroxybutyl ester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid according to WO 98/25918

A mixture of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (0.32 g, 1.4 mmol), 4-N,N-dimethylamino pyridine (16 mg, 0.13 mmol), 4-nitroxybutan-1-ol (0.34 g, 2.5 mmol) in dichloromethane (6 ml) at a temperature in the range 0°C-5°C is added, under stirring, to a solution of N,N'-dicyclohexylcarbodiimide (0.29 g, 1.4 mmol) in dichloromethane (6 ml). The mixture is left under stirring at the same temperature for 3 hours and then dried by solvent evaporation under vacuum. The residue is purified by chromatography on silica gel column (eluent dichloromethane) to give the 4-nitroxybutyl ester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (0.41 g, 1.19 mmol, yield 85%) in the form of an oil. HPLC purity: 98%.

^1H NMR(CDCl₃) δ (ppm): 1.59 (d, 3H, J=7.5 Hz); 1.65 (m, 4H); 3.85 (q, 1H, J=7.5 Hz); 3.91 (m, 2H); 4.10 (m, 2H); 7.1-7.7

(m, aromatic, 8H).

Enantiomeric excess: 94%.

EXAMPLE 2

To a solution of 4-nitroxybutan-1-ol (2.0 g; 14.8 mmol) in dichloromethane (20 ml), cooled at 0°C-5°C, potassium carbonate (3.21 g, 23.2 mmol) is added under stirring.

To the mixture a solution of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid chloride (3.86 g, 15.5 mmol; enantiomeric excess 98%) in dichloromethane (22 ml) is added, maintaining the temperature in the range 10°C-15°C. When the addition is over the temperature is increased and maintained for 10 hours at a value in the range 15°C-20°C and then the solution is filtered. The solvent is evaporated under vacuum. The residue is purified by chromatography on silica gel column (eluent dichloromethane) to give the 4-nitroxybutyl ester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (4.4 g, 12.6 mmol, yield 85%) in the form of an oil. HPLC purity: 99%.

¹H NMR(CDCl₃) δ (ppm): 1.59 (d, 3H, J=7.5 Hz); 1.65 (m, 4H); 3.85 (q, 1H, J=7.5 Hz); 3.91 (m, 2H); 4.10 (m, 2H); 7.1-7.7 (m, aromatic, 8H).

Enantiomeric excess: 98%.

EXAMPLE 3

Example 2 is repeated using toluene as solvent. The nitroxyester yield is 76%, the (HPLC) purity > 99%. The enantiomeric excess is equal to 98%.

EXAMPLE 4

Example 2 is repeated but using as a base calcium carbonate. 4.6 g, equal to 13.3 mmols of nitroxyester (yield 90%) are obtained, HPLC purity >99%, enantiomeric excess 98%.

EXAMPLE 5

Example 2 is repeated but using as a base calcium aluminosilicate. 4.6 g, equal to 13.3 mmols of nitroxyester (yield 90%) are obtained, HPLC purity >99%, enantiomeric excess 98%.

EXAMPLE 6

To a solution of 4-nitroxybutan-1-ol (2.0 g; 14.8 mmols) in dichloromethane (20 ml), cooled at a temperature in the range 0°C-5°C, potassium carbonate (3.21 g, 23.2 mmols) is added under stirring.

To the mixture a solution of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid chloride (3.86 g, 15.5 mmols, enantiomeric excess 98%) in dichloromethane (22 ml) is added, maintaining the temperature in the range 10°C-15°C. When the addition is over, the temperature is increased to a value in the range 15°C-20°C for 10 hours and then the solution is filtered. Water (1 ml) and N,N-dimethylformamide (2 ml) are added to the solution and left under stirring at room temperature for 3 hours. At the end the organic phase is separated, washed with water and filtered through a potassium carbonate panel. The solvent is evaporated under vacuum and 4.1 g, equivalent to 11.8 mmols of ester (yield 80%) in the form of an oil, are

obtained, HPLC purity >99%, enantiomeric excess 98%.

EXAMPLE 7 (comparative)

Example 2 is repeated but using as a base triethylamine. The obtained mixture after the reaction is analyzed to evaluate the enantiomeric excess, which results equal to 80%.

EXAMPLE 8 (comparative)

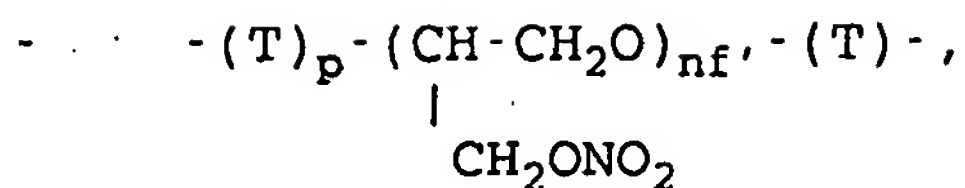
Example 2 is repeated but using as a base diisopropylethylamine. The mixture obtained after the reaction is analyzed to evaluate the enantiomeric excess, which results equal to 76%.

EXAMPLE 9 (comparative)

Example 2 is repeated but using as a base N-methylmorpholine. The mixture obtained after the reaction is analyzed to evaluate the enantiomeric excess, which results equal to 56%.

CLAIMS

1. A process for obtaining nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid having an enantiomeric excess higher than or equal to 97%, preferably higher than or equal to 98%, characterized in that an halide of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula A-Hal, wherein A is the acyl residue of the acid, is let react in an inert organic solvent with an aliphatic nitroxyalkanol HO-Y-ONO₂, wherein Y has one of the following meanings:
 - a linear or optionally branched C₁-C₂₀, preferably C₂-C₅, alkylene, or
 - a cycloalkylene with ring from 3 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, said cycloalkylene optionally substituted with one or two alkylenes as above defined, and/or with one or more alkyl radicals having in the chain a number of carbon atoms as above defined for alkylene;
 - an aromatic residue with ring having 5 or 6 carbon atoms, said aromatic residue optionally substituted with one or two alkylenes as above defined, and/or with one or more alkyl radicals having in the chain a number of carbon atoms as above defined for alkylene, or a -COOH group;



T being alkylene as above defined and p an integer equal to zero or one, alkylene having the above mentioned meaning, nf' is an integer from 1 to 6, preferably from 1 to 4;

in the presence of an inorganic base, to give the corresponding nitroxyalkylester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula A-O-Y-ONO₂, wherein A and Y are as above defined.

2. A process according to claim 1, wherein the aliphatic nitroxyalcohol amount on molar basis is in the range 1-2, preferably 1.2-1.5, with respect to that of the acid halide.
3. A process according to claims 1 and 2, wherein the inorganic bases are hydroxides, oxides, carbonates and bicarbonates, silicates, aluminosilicates of the alkaline and alkaline-earth metals, or hydroxides, oxides, carbonates and bicarbonates of metals belonging to the group IIB, preferably zinc, or to groups IIIa or IVa, preferably tin.
4. A process according to claims 1-3, wherein the inorganic base amount is in molar ratio with the acid halide amount in the range 1-2, preferably 1.2-1.5.

5. A process according to claims 1-4, wherein the reaction is carried out at a temperature in the range -20°C and 50°C, preferably 0°C and 20°C.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/07222

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IPC 7 C07C203/04

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B. FIELDS SEARCHED

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IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 97 16405 A (NICOX SA) 9 May 1997 (1997-05-09) example 3 ---	1-5
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☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

9 November 2000

Date of mailing of the international search report

24/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo-nt,
Fax: (+31-70) 340-3016

Authorized officer

Bonnevalle, E

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/EP 00/07222

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 09831 A (NICOX LTD) 13 April 1995 (1995-04-13) example 1 -----	1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. onal Application No

PCT/EP 00/07222

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 February 2001 (22.02.2001)

PCT

(10) International Publication Number
WO 01/12584 A2

(51) International Patent Classification⁷: C07C 219/14, 219/30, 229/42, 233/25, C07D 219/10, 295/08, 309/30, 401/12, 471/04, 495/04, 499/68, C07H 15/252, A61K 31/21, C07D 495/00, 333/00, 213/00

(74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni, 2, I-20129 Milano (IT).

(21) International Application Number: PCT/EP00/07225

(22) International Filing Date: 27 July 2000 (27.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI99A001817 12 August 1999 (12.08.1999) IT

(81) Designated States (*national*): AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— Without international search report and to be republished upon receipt of that report.

(71) Applicant (*for all designated States except US*): NICOX S.A. [FR/FR]; 45, Avenue Kléber, F-75116 Paris (FR).

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I-20052 Monza (IT).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL COMPOUNDS

(57) Abstract: Compounds or their salts of general formula (I): A-B-N(O)_s, wherein: s is an integer equal to 1 or 2; A = R-T₁-, wherein R is the drug radical and T₁ = (CO)_t or (X)_{t'}, wherein X = O, S, NR_{1c}, R_{1c} is H or a linear or branched alkyl or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1; B = -T_B-X₂-O- wherein T_B = (CO) when t = 0, T_B = X when t' = 0, X being as above defined; X₂, bivalent radical, is such that the precursor drug of A and the precursor of B meet respectively the pharmacological tests described in the description.

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PHARMACEUTICAL COMPOUNDS

The present invention relates to novel drugs for systemic use and non systemic use, and the composition thereof, to be used in oxidative stress and/or endothelial dysfunctions of moderate intensity.

By oxidative stress it is meant the generation of free radicals or radicalic compounds, which causes injury both of the cell and that of the surrounding tissue (Pathophysiology: the biological basis for disease in adults and children, McCance & Huether 1998 pages 48-54).

By endothelial dysfunctions it is meant those relating to the vasal endothelium. The damage of the vasal endothelium is known as one of those important events that can cause a series of pathological processes affecting various organs and body apparatuses, as described hereinafter (Pathophysiology: The biological basis for disease in adults and children, McCance & Huether 1998 page 1025).

As known, the oxidative stress and/or the endothelial dysfunctions are associated to various pathologies as reported hereinafter. The oxidative stress can also be caused by toxicity of a great variety of drugs, which significantly affects their performances.

Said pathological events are of a chronic, debilitating character and are very often typical of the elderly. As already said, in said pathological conditions the drugs used show a remarkably worsened performance.

Examples of pathological situations caused by the oxidative stress and/or by the endothelial dysfunctions, or present in elderly, are the following:

- For the cardiovascular system: myocardial and vascular ischaemia in general, hypertension, stroke, arteriosclerosis, etc.
- For the connective tissue: rheumatoid arthritis and connected inflammatory diseases, etc.
- For the pulmonary system: asthma and connected inflammatory diseases, etc.
- For the gastrointestinal system: ulcerative and non ulcerative dyspepsias, intestinal inflammatory diseases, etc.

- For the central nervous system: Alzheimer disease, etc.
- For the urogenital system: impotence, incontinence.
- For the cutaneous system: eczema, neurodermatitis, acne.
- The infective diseases in general (ref.: Schwarz-KB, Brady "Oxidative stress during viral infection: A review" Free radical Biol. Med. 21/5, 641-649 1996).

Further, the ageing process can be considered as a true pathologic condition (ref. Pathophysiology: the biological basis for disease in adults and children, pages 71-77).

The known drugs when administered to patients having pathologies associated to oxidative stress and/or endothelial dysfunctions, show a lower activity and/or higher toxicity.

This happens for example for drugs such as the antiinflammatory, cardiovascular drugs, respiratory apparatus drugs, central nervous system drugs, bone system drugs, antibiotics, urogenital, endocrine drugs, etc.

Drug research is directed to find new molecules having an improved therapeutic index (efficacy/toxicity ratio) or a lower risk/benefit ratio, also for pathological conditions as those above mentioned, wherein the therapeutic index of a great number of drugs results lowered. In fact in the above mentioned conditions of oxidative stress and/or endothelial dysfunctions, many drugs show a lower activity and/or higher toxicity.

For instance antiinflammatory drugs, such as NSAIDs and anticolitic drugs, such as 5-aminosalicylic acid and its derivatives, show the following drawbacks. NSAIDs result toxic particularly when the organism is debilitated or affected by morbid conditions associated to oxidative stress. Said conditions are for example the following: age, pre-existing ulcer, pre-existing gastric bleeding, debilitating chronic diseases such as in particular those affecting cardiovascular, renal apparatuses, the haematic crisis, etc. ("Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving non-steroidal anti-inflammatory drugs. A randomized, double blind, placebo-controlled trial." F.E. Silverstein et Al., Ann. Intern. Med. 123/4, 241-9, 1995; Martindale 31a ed. 1996, pag. 73, Current Medical Diagnosis and Treatment 1998, pages 431 and 794).

The administration of anti-inflammatory drugs to patients

in the above mentioned pathological conditions can be made only at doses lower than those used in therapy in order to avoid remarkable toxicity phenomena. Thus anti-inflammatory activity results poor.

Beta-blockers, used for the angina, hypertension and cardiac arrhythmia treatment, show side effects towards the respiratory apparatus (dyspnoea, bronchoconstriction), and therefore they can give problems in patients affected by pathologies to said organs (asthma, bronchitis). Therefore beta-blockers further worsen respiratory diseases such as asthma. Therefore in asthmatic patients reduced doses of said drugs must be used in order not to jeopardize even more the respiratory functionality. Thus the efficacy of the beta-blockers results very reduced.

Antithrombotics, such as for example dipyridamole, aspirin, etc., used for the prophylaxis of thrombotic phenomena, have the same drawbacks. In patients affected by pathologies connected to oxidative stress and/or endothelial dysfunctions, the therapeutic action or the tolerability of these drugs, as in the case of aspirin, is greatly reduced.

Bronchodilators for example salbutamol, etc., are used in the asthma and bronchitis treatment and drugs active on the cholinergic system are used in pathologies such as urinary cholinergic incontinence. Their administration can produce similar side effects affecting the cardiovascular apparatus, causing problems both to cardiopathic and to hypertensive patients. Cardiopathies and hypertension are pathologies associated, as above said, to the oxidative stress and/or endothelial dysfunctions. Also these drugs show the same drawbacks as those above mentioned.

Expectorant and mucolytic drugs, which are used in the therapy of inflammatory states of the respiratory organs, show drawbacks in patients affected by the above described conditions. Their administration can give rise to heartburn and gastric irritability, particularly in the elderly.

Bone resorption inhibitors, such as diphosphonates (for example alendronate, etc.) are drugs showing high gastrointestinal toxicity. Therefore also these drugs can show the same drawbacks as those above mentioned.

Phosphodiesterase inhibitors, such as for example sildenafil, zaprinast, used in the cardiovascular and respiratory system diseases, are characterized by similar problems as to tolerability and/or efficacy in the mentioned pathological conditions of oxidative stress and/or endothelial disfunctions.

Antiallergic drugs, for example cetirizine, montelukast, etc. show similar problems in the mentioned pathological conditions, particularly for that it concerns their efficacy.

Anti-angiotensin drugs, f.i. ACE-inhibitors, for example enalapril, captopril, etc., and receptor inhibitors, for example losartan, etc., are used in the cardiovascular disease treatment. Their drawback is to give side effects to the respiratory apparatus (i.e. cough, etc.) in the above mentioned pathological conditions.

Antidiabetic drugs, both of the insulin-sensitizing and of hypoglycaemizing type, such as for example sulphonylureas, tolbutamide, glypiride, glyclazide, glyburide, nicotinamide etc., are ineffective in the prophylaxis of diabetic complications. Their administration can give side effects, such as for example gastric lesions. These phenomena become more intense in the pathological conditions above mentioned.

Antibiotics, for example ampicillin, clarithromycin, etc., and antiviral drugs, acyclovir, etc., show problems as regards their tolerability, for example they cause gastrointestinal irritability.

Antitumoral drugs, for example doxorubicine, daunorubicin, cisplatinum, etc., have high toxicity, towards different organs, among which are stomach and intestine. Said toxicity is further worsened in the above mentioned pathologies of oxidative stress and/or endothelial dysfunctions.

Antidementia drugs for example nicotine and colino-mimetics, are characterized by a poor tolerability especially in the above mentioned pathologies.

Drugs having a steroidal structure which are used in the therapy of acute diseases (asthma, etc.) or chronic diseases (intestinal, hepatic, respiratory diseases, female reproductive apparatus diseases, hormonal dysfunctions, cutaneous diseases, etc.) are characterized by remarkable toxic effects affecting

various organs, particularly in the above mentioned oxidative stress conditions.

This class of steroidal drugs, among which hydrocortisone, cortisone, prednisone, prednisolone, fludrocortisone, desoxycorticosterone, methylprednisolone, triamcinolone, paramethasone, betamethasone, dexamethasone, triamcinolone acetonide, fluocinolone acetonide, beclomethasone, acetoxypregnelone, etc., has remarkable farmaco-toxicological effects on various organs and for this reason the clinical use and its interruption cause a series of side effects, some of which very serious. See for example Goodman & Gilman, "The pharmaceutical Basis of Therapeutics" 9^{ed.}, pag. 1459-1465, 1996.

Among these toxic effects it can be mentioned: those affecting the bone tissue leading to an altered cellular metabolism and high osteoporosis incidence; those affecting the cardiovascular system generating hypertensive responses; those affecting the gastrointestinal apparatus giving gastric damages.

See for example Martindale "The extrapharmacopoeia", 30th ed., pag. 712-723, 1993.

Also biliary acids, which are used in hepatic trouble therapy and in biliary colics, belong to steroidal drugs. The ursodesoxycholic acid is also used in some hepatic troubles (hepatic cirrhosis of biliary origin, etc.). Their tolerability is strongly worsened in the presence of gastrointestinal complications (chronic hepatic damage, peptic ulcer, intestinal inflammation, etc.). Also in the case of biliary acids the oxidative stress notably affects the product performance: both the efficacy and the tolerability of the chenodeoxycholic and ursodesoxycholic acids are meaningfully reduced. In particular the undesired effects affecting liver result exalted. Among steroidal structures also estrogens used for the dislipidaemia, hormonal troubles, female apparatus tumours treatment can be mentioned. Also these steroids show side effects as above mentioned, in particular at hepatic level.

According to the above mentioned prior art, it seems almost impossible to separate therapeutic actions from side effects, see Goodman et al, above mentioned, at p. 1474.

The need was felt to have available drugs showing an

improved therapeutic performance, i.e. endowed both of a lower toxicity and/or higher efficacy, so that they could be administered to patients in morbid conditions of oxidative stress and/or endothelial dysfunctions of moderate intensity, without showing the drawbacks of the drugs of the prior art.

It has now surprisingly and unexpectedly found that the aforementioned problems evidenced following the administration of drugs, to patients affected by oxidative stress and/or endothelial dysfunctions, or to the elderly in general, are solved by a novel class of drugs as described hereinafter.

An object of the invention are compounds or their salts having the following general formula (I):



wherein:

s is an integer equal to 1 or 2, preferably s = 2;

A = R—T₁—, wherein

R is the drug radical and

T₁ = (CO)_t or (X)_t, wherein X = O, S, NR_{1c}, R_{1c} is H or a linear or branched alkyl, having from 1 to 6 carbon atoms, or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = —T_B—X₂—O— wherein

T_B = (CO) when t = 0, T_B = X when t' = 0, X being as above defined;

X₂, bivalent radical, is such that the corresponding precursor of B does not meet test 5 and meets test 4A; said precursor having formula —T_B—X₂—OH, wherein T_B = (CO) and t = 0, the free valence of T_B is saturated with:

—OZ wherein Z = H or R_{1a}, R_{1a} being linear or branched when possible C₁-C₁₀ alkyl, preferably C₁-C₅, or with —Z^I-N-Z^{II}, Z^I and Z^{II} being equal or different from each other, having the Z values, when T_B = X and t' = 0, the free valence of T_B is saturated with H;

with the proviso that:

the drug A = R—T₁—, wherein the free valence is saturated as hereinafter mentioned:

- when $t' = 0$ with:
 - O-Z wherein Z = H or R_{1a} as above defined, or with
 - Z^I-N-Z^{II} ,
|
 Z^I and Z^{II} being as above defined,
- when $t = 0$ with X-Z, wherein X and Z as above defined,

is such as to meet at least one of tests 1-3;

- wherein test 1 (NEM) is a test in vivo carried out on four groups of rats (each formed by 10 rats), the controls (two groups) and the treated (two groups) of which one group of the controls and one group of the treated respectively are administered with one dose of 25 mg/kg s.c. of N-ethylmaleimide (NEM), the controls being treated with the carrier and the treated groups with the carrier + the drug of formula $A = R-T_1$ wherein the free valence is saturated as above indicated, administering the drug at a dose equivalent to the maximum one tolerated by the rats that did not receive NEM, i.e. the highest dose administrable to the animal at which there is no manifest toxicity, i.e. such as to be symptomatologically observable; the drug complies with test 1, i.e. the drug can be used to prepare the compounds of general formula (I), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in the group treated with NEM + carrier + drug are observed gastrointestinal damages greater than those of the group treated with the carrier, or of the group treated with the carrier + drug, or of the group treated with the carrier + NEM;

- wherein test 2 (CIP) is a test in vitro wherein human endothelial cells from the umbilical vein are harvested under standard conditions, then divided into two groups (each group replicated five times), of which one is treated with a mixture of the drug 10^{-4} M concentration in the culture medium, the other group with the carrier; then cumene hydroperoxide (CIP) having a 5 mM concentration in the culture medium is added to each of the two groups; the drug meets test 2, i.e. the drug can be used to prepare the compounds of general formula (I), if a statistically significant inhibition of the apoptosis (cellular damage) induced by CIP is not obtained with $p < 0.01$ with respect to the group treated with the carrier and CIP;

- wherein test 3 (L-NAME) is a test in vivo carried out on four groups of rats (each group formed by 10 rats) for 4 weeks and receiving drinking water, the controls (two groups) and the treated (two groups), of which one group of the controls and of the treated respectively receives in the above 4 weeks drinking water added of N- ω -nitro-L-arginine methyl ester (L-NAME) at a concentration of 400 mg/litre, the controls in the 4 weeks being administered with the carrier and the treated in the 4 weeks with the carrier + the drug, administering the carrier or the drug + carrier once a day, the drug being administered at the maximum dose tolerated by the group of rats not pretreated with L-NAME, i.e., the highest dose administrable to animals at which no manifest toxicity appears, i.e. such as to be symptomatologically observable; after the said 4 weeks, the water supply is stopped for 24 hours and then sacrificed, determining the blood pressure 1 hour before sacrifice, and after sacrifice of the rats determining the plasma glutamic pyruvic transaminase (GPT) after sacrifice, and examining the gastric tissue; the drug meets test 3, i.e. the drug can be used to prepare the compounds of general formula (I), when in the group of rats treated with L-NAME + carrier + drug, greater hepatic damages (determined as higher values of GPT) and/or gastric and/or cardiovascular damages (determined as higher values of blood-pressure) are found in comparison respectively with the group treated with the carrier alone, or with the group treated with the carrier + drug, or with the group treated with the carrier + L-NAME;

- wherein test 4A which must be met by the compound precursor of B is a test in vitro wherein a portion of an erythrocyte suspension formerly kept at 4°C for 4 days, said erythrocytes isolated by standard procedures from Wistar male rats and suspended in a physiological solution buffered at pH 7.4 with phosphate buffer, is centrifuged at 1000 rpm for 5 minutes and 0.1 ml of the centrifuged erythrocytes are diluted with sodium phosphate buffer pH 7.4 at 50 ml; aliquots of 3,5 ml each (No. 5 samples) are taken from said diluted suspension and incubated at 37°C in the presence of cumene hydroperoxide at a concentration 270 μ M and the suspension turbidity determined at 710 nm at intervals of 30 minutes to establish

the time (Tmax) at which occurs the maximum turbidity, that corresponds to the maximum amounts of cells lysed by cumene hydroperoxide (haemolysis assumed to be = 100%); then alcoholic solutions of the compounds precursors of B are added to 3.5 ml aliquots of the diluted suspension of centrifuged erythrocytes (tests carried out on 5 samples for each precursor of B assayed) in order to have a final concentration 2 mM of the precursor of B and then the resulting suspension preincubated for 30 minutes, cumene hydroperoxide is added in a quantity to have the same above indicated final concentration and at Tmax is determined the percentage of haemolysis inhibition in the sample from the ratio, multiplied by 100, between the absorbance of the sample containing the erythrocytes, the precursor of B and cumene hydroperoxide respectively and that of the sample containing the erythrocytes and cumene hydroperoxide; the precursors of B meet the test if they inhibit the haemolysis induced by cumene hydroperoxide by a percentage > 15%;

- wherein test 5 which must not be met by the precursor compound of B is an analytical determination carried out by adding aliquots of 10^{-4} M methanol solutions of the precursor of B, to a solution formed by admixing a 2 mM solution of desoxyribose in water with 100 mM of phosphate buffer and 1 mM of the salt $\text{Fe}^{\text{II}}(\text{NH}_4)_2(\text{SO}_4)_2$; after having thermostatted the solution at 37°C for one hour are added, in the order, aliquots of aqueous solutions of trichloroacetic acid 2.8% and of thiobarbituric acid 0.5 M, heating is effected at 100°C for 15 minutes and the absorbance of the tested solutions is then read at 532 nm; the inhibition induced by the precursor of B in the confront of radical production by Fe^{II} is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound and the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage as above defined of the precursor of B is higher than or equal to 50%; provided that in formula (I) when X_2 of B is a linear or branched $C_1 - C_{20}$ alkylene or a cycloalkylene having from 5 to

7 carbon atoms optionally substituted, the drugs of formula $A = R-T_1$ - with the free valence saturated as above described, used in the compound of formula (I), has not to belong to the following classes: drugs for use in incontinence, antithrombotic drugs (ACE inhibitors), prostaglandins, antiinflammatory drugs (NSAIDS and corticosteroids) but not excluding from the antiinflammatory NSAIDS paracetamol and sulindac.

In the formula $-T_B-X_2-O-$ of the precursor compound of B which meets test 4A and does not meet test 5, compounds wherein X_2 is equal to the $R_{1B}-X-R_{2B}$ radical wherein R_{1B} and R_{2B} , equal to or different from each other, are linear or branched C_1-C_6 alkylenes, can be used, or X_2 is a radical wherein two alkylene chains C_1-C_4 , preferably C_1-C_2 , are linked to non adjacent positions of a central ring having 4 or 6 atoms, preferably 5 or 6 atoms, said ring being an unsaturated cycloaliphatic ring, or a saturated or aromatic eterocyclic ring, containing one or two heteroatoms, equal or different, selected from O, S, N. By unsaturated cycloaliphatic ring it is meant a ring that has not an aromatic character according to the Hückel's rule.

Other examples of precursor compounds of B are: 1,4-butanediol: $HO-(CH_2)_4-OH$, 6-hydroxyhexanoic acid: $HO-(CH_2)_5-COOH$, 4-hydroxybutyric acid: $HO-(CH_2)_3-COOH$, N-methyldiethanolamine: $HO-(CH_2)_2-N(CH_3)-(CH_2)_2-OH$, diethylenglycol: $HO-(CH_2)_2-O-(CH_2)_2-OH$, thiodiethylenglycol: $HO-(CH_2)_2-S-(CH_2)_2-OH$; 1,4 dioxane-2,6-dimethanol, tetrahydropyran-2,6-dimethanol, 4H pyran-2,6-dimethanol, tetrahydrothiopyran-2,6-dimethanol, 1,4-dithiane-2,6-dimethanol, cyclohexene-1,5-dimethanol, thiazole-2,5-dimethanol, thiophene-2,5-dimethanol, oxazole-2,5-dimethanol, preferably N-methyldiethanolamine, diethylenglycol, thiodiethylenglycol.

The precursor compounds of the drug and of B are prepared according to the known methods in the prior art and described, for example, in "The Merck Index, 12a Ed. (1996), herein incorporated by reference.

The tests conducted to identify the drug corresponding to the R radical of the formula (I) are in detail the following:

Test 1 (NEM): evaluation of the gastrointestinal damage from oxidative stress induced by free radicals formed following

administration of N-ethylmaleimide (NEM) (H.G. Utley, F. Bernheim, P. Hochstein "Effects of sulphhydryl reagents on peroxidation in microsomes" Archiv. Biochem. Biophys. 118, 29-32 1967).

The animals (rats) are distributed in the following groups (no. 10 animals for group):

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, or a physiologic solution when parenterally administered, i.e. by subcutaneous, intraperitoneal, intravenous or intermuscular route),

2° group: treatment: carrier as above defined + NEM,

B) Groups treated with the drug:

group I: treatment: carrier + drug,

gruppo II: treatment: carrier + drug + NEM.

The administration routes are those known for the drug, and can be the oral or subcutaneous, intraperitoneal, intravenous or intramuscular route.

The NEM dose is of 25 mg/kg in physiologic solution (subcutaneous route) and the drug is administered one hour later, in suspension in the carrier, as a single dose which corresponds to the maximum one, or the highest still tolerated by the animals of the group of rats not pretreated with NEM, i.e. the highest administrable dose to said group at which there is no manifest toxicity in the animals, defined as a toxicity that is clearly recognizable for its symptoms. The animals are sacrificed after 24 hours and then one proceeds to the evaluation of the damage to the gastrointestinal mucosa.

The drug meets test 1, i.e. it can be used to prepare the compounds of general formula (I), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in said group the gastrointestinal damages noticed are greater than those shown by the group treated with the carrier alone, or the group treated with carrier + drug, or the group treated with carrier + NEM, even though the drug pharmacotherapeutic efficacy, assayed by using specific tests, is not significantly reduced.

Test 2 (CIP): Protection parameter of endothelial cell

against the oxidative stress induced by cumene hydroperoxide (CIP).

Human endothelial cells of the umbilical vein are prepared according to an usual standard procedure. Fresh umbilical veins are filled with a 0.1% by weight collagenase solution and incubated at 37°C for 5 minutes.

Afterwards the veins are perfused with medium M 199 (GIBCO, Grand Island, NY) pH 7.4 further added of other substances, as described in the examples. The cells are collected from the perfusate by centrifugation and harvested in culture flasks T-75, pretreated with human fibronectin. The cells are then harvested in the same medium, further added with 10 ng/ml of bovine hypothalamic growth factor. When the cells of the primary cell culture (i.e. that directly obtained from ex-vivo) form a single layer of confluent cells (about 8,000,000 cells/flask), the culture is stopped and the layers washed and trypsinized. The cellular suspensions are transferred into the wells of a cell culture plate having 24 wells, half of which is then additioned with the same culture medium containing the drug at a 10^{-4} M concentration, and harvested in a thermostat at 37°C at a constant moisture. Only the cells coming from said first sub-cultures are used for the experiments with cumene hydroperoxide (CIP). The cells are identified as endothelial cells by morphological examination and by their specific immunological reaction towards factor VIII; said cultures did not show any contaminations from myocytes or fibroblasts.

Before starting the test, the cellular culture medium is removed and the cellular layers are carefully washed with a physiologic solution at a temperature of 37°C. The wells of the culture plate are then incubated for one hour with CIP at a 5 mM concentration in the culture medium. The evaluation of cellular damage (apoptosis) is carried out by determining the per cent variation of the DNA fragmentation with respect to the control group (treated with CIP alone), evaluating the fluorescence variation at the wave length of 405-450 nm. 5 replicates for each sample are carried out.

The drug meets the test, i.e. it can be used for preparing the compounds of general formula (I), when a statistically significant inhibition of apoptosis (cellular damage) induced

by CIP with respect to the group treated with CIP alone is not obtained at $p < 0.01$.

Test 3 (L-NAME): evaluation of the endothelial dysfunction induced by administration of L-NAME (N^W -nitro-L-arginine-methyl ester). J. Clin. Investigation 90, 278-281, 1992.

The endothelial dysfunction is evaluated by determining the damage to the gastrointestinal mucosa, the hepatic damage and blood hypertension induced by administration of L-NAME.

The animals (rats) are divided in groups as herein below shown. The group receiving L-NAME is treated for 4 weeks with said compound dissolved at a concentration of 400 mg/litre in drinking water. The following groups are constituted (No. 10 animals for group):

A) Control groups:

1° group: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, physiologic solution when administered parenterally),

2° group: carrier + L-NAME,

B) Groups administered with the drug:

3° group: carrier + drug,

4° group: carrier + drug + L-NAME.

The administration routes are those known for the drug, and can be the oral or subcutaneous, intraperitoneal, intravenous or intramuscular route. The drug is administered at that dose which results the highest still tolerated by the animals of the group of rats not pretreated with L-NAME, i.e. the highest administrable dose at which there is no evident toxicity in the animals, i.e. a toxicity recognizable for its symptoms. The drug is administered once a day for 4 weeks.

At the end of the four weeks treatment access to water is prevented and after 24 hours the animals are sacrificed.

One hour before the sacrifice blood-pressure is determined, and a blood pressure increase is taken as an evaluation of the damage to vascular endothelium. The damage to the gastric mucosa is evaluated as illustrated in test 1 (see example F1). The hepatic damage is determined by evaluation of the glutamic-pyruvic transaminase (GPT increase) after sacrifice.

The drug meets test 3, i.e. it can be used for preparing the compounds of general formula (I), when in the group of rats treated with L-NAME + drug + carrier it is found an higher hepatic damage (GPT) and/or an higher gastric damage and/or an higher cardiovascular (blood-pressure) damage in comparison to that of the group treated with the carrier alone, or of the group treated with carrier + drug, or of the group treated with carrier + L-NAME; even if the drug pharmacotherapeutic efficacy, assayed by specific tests, is not significantly reduced.

Under the conditions indicated in the above described in vivo tests 1 and 3 the therapeutic index of the drug is reduced since the usual doses at which the drug can be effective are no longer tolerated.

Test 4A is performed according to the method described by R. Maffei Facino, M Carini G. Aldini, M.T. Calloni, Drugs Exptl. Clin. Res. XXIII (5/8) 157-165 1997. Test 4A is a test in vitro wherein erythrocytes isolated by standard methods from Wister male rats (Charles River), are kept for 4 days at 4°C in suspension in a physiological solution buffered at pH 7.4 with phosphate buffer. At the end of said period an aliquot of the suspension is taken and centrifuged at 1000 rpm for 5 minutes. 0.1 ml of the centrifuged erythrocytes are diluted to 50 ml with sodium phosphate buffer pH 7.4, obtaining a suspension of erythrocytes 0.2% by volume. No. 5 aliquots of 3.5 ml each of the diluted suspension are added of 0.1-0.3 ml of an alcoholic solution of cumene hydroperoxide in order to have a 270 µM concentration and then incubated at 37°C. This compound causes cell lysis, said lysis causing an increase of turbidity of the suspension. Cell lysis progress is followed by turbidimetry at 710 nm. By performing readings of optical density (or transmittance) at intervals of 30 minutes, it is determined the time (Tmax) at which there is the maximum of turbidity in the suspension, that corresponds to the maximum amount of cells lysed in the suspension. Tmax is assumed to be the time corresponding to 100% of erythrocyte lysis. For determining the inhibiting effect of the precursors of B on haemolysis induced by cumene hydroperoxide, 0.1-0.2 ml of ethanol solutions of each of the assayed compounds precursors

of B are added to 3.5 ml aliquots of the suspension of centrifuged erythrocytes (No. 5 samples for each compound) in order to have a 2 mM final concentration, and preincubated for 30 minutes. Cumene hydroperoxide is then added in such a quantity to have the same final previously stated molarity, and the percentage of haemolysis inhibition of the compound at T_{max} is determined as the ratio, multiplied by 100, between the absorbance given by the suspension of the sample under assay, containing the erythrocytes, the precursor of B and cumene hydroperoxide respectively, and the absorbance of the suspension containing the erythrocytes and cumene hydroperoxide; the compound precursor of B meets test 4A if it inhibits the haemolysis induced by cumene hydroperoxide by a percentage > 15%;

Test 5 is a colorimetric test wherein 0.1 ml aliquots of 10⁻⁴ M methanolic solutions of the tested products are added to test tubes containing a solution formed by 0.2 ml of 2 mM desoxyribose, 0.4 ml of phosphate buffer pH 7.4 100 mM and 0.1 ml of 1 mM Fe^{II}(NH₄)₂(SO₄)₂ in 2mM HCl. The test tubes are then maintained at 37°C for one hour. Then in each test tube 0.5 ml of a 2.8% solution in trichloroacetic acid water and 0.5 ml of an aqueous 0.1 M solution of thiobarbituric acid are added, in the order. A reference blank is formed by adding to a test tube containing only the above described aqueous solution of reactants 0.1 ml of methanol. The test tubes are closed and heated in an oil bath at 100°C for 15 minutes. A pink coloration is developed the intensity of which is proportional to the quantity of desoxyribose undergone to radical oxidative degradation. The solutions are cooled at room temperature and their absorbances are read at 532 nm against the blank. The inhibition induced by the precursor of B or B₁ or C = -T_C-Y-H in the confront of radical production by Fe^{II} is determined by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound + the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage of radical production as above defined from the precursor of B is higher

than or equal to 50%. The compound precursor of B according to the present invention does not meet test 5.

Unexpectedly the invention products of formula (I) have an improved therapeutic index, under oxidative stress conditions, compared with the precursor drugs. The compounds of the invention of formula (I) wherein the compound precursor of B meets test 4A but does not meet test 5 can be used, as above said, as drugs for the therapy of moderate oxidative stress conditions. In this sense according to the present invention, are intended conditions of moderate oxidative stress.

For illustrative purposes the above mentioned tests are referred to the following compounds. See the Tables.

Test 1: precursor drug: indomethacin

- Maximum administrable dose to rats: 7.5 mg/Kg p.o. By administering a higher dose a toxicity is manifested, characterized by enteropathy, tremor, sedation until death (within 24 hours).
- The group of rats treated with NEM + indomethacin at the above mentioned dose shows gastrointestinal damages.

Since indomethacin in the groups treated with NEM causes gastrointestinal damages, it meets test 1. Indomethacin can therefore be used as a drug for preparing the compounds (I) of the present invention.

Test 2: precursor drugs: indomethacin, paracetamol and mesalamine

Indomethacin and paracetamol meet test 2 since the cellular damage (apoptosis) inhibition induced by CIP is not significantly different with respect to that of the controls.

Therefore the above drugs can be used as drugs for preparing the compounds (I) of the present invention.

On the contrary mesalamine does not meet test 2, since it inhibits the apoptosis induced by CIP. Therefore mesalamine according to test 2 could not be used as a precursor to prepare the compounds (I) of the present invention. It has been however found that mesalamine submitted to test 1 causes gastrointestinal damages.

Thus also mesalamine can be used as a precursor for preparing the compounds (I) of the present invention.

Test 3 (L-NAME) precursors drugs: paracetamol, simvastatin, omeprazole

Paracetamol and simvastatin meet test 3 since they cause gastric and hepatic damages greater than those induced both by L-NAME + carrier and by the drug + carrier.

Therefore they can be used as precursors to prepare the compounds (I) of the present invention.

On the contrary it has been found that omeprazole neither causes gastric nor hepatic damages, nor influences blood-pressure. According to test 3 omeprazole could not be used as a precursor for preparing the compounds (I) of the present invention.

Test 4A (test for the precursor of B)

N-methyldiethanolamine shows an inhibition of 54.4% (Table V) of haemolysis induced by cumene hydroperoxide. Therefore it meets test 4A and can be used as precursor of B if it does not meet test 5.

Diethanolamine does not inhibit haemolysis induced by cumene hydroperoxide, and it does not meet test 4A. Therefore this compound cannot be used as precursor of B.

Test 5 (test for the precursor of B)

The Table III relating to said test illustrates that N-methyldiethanolamine does not meet test 5, since it does not inhibit radical production from Fe^{II} . Therefore it can be used as precursor of B.

The compounds of formula (I) according to the present invention can be transformed into the corresponding salts. For example a method for forming salts is the following. When in the molecule of the formula (I) compounds a nitrogen atom is present sufficiently basic so as to be salified, the corresponding salts of said compounds are obtainable by reaction in organic solvent such as for example acetonitrile, tetrahydrofuran with an equimolecular amount of the corresponding organic or inorganic acid.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acids.

Examples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acids.

The derivatives according to the invention can be used in

the therapeutic indications of the precursor drug, allowing to obtain the other advantages exemplified hereinafter for some groups of these drugs:

- Anti-inflammatory drugs NSAIDs: the invention compounds result very well tolerated and effective, even when the organism is debilitated and is under conditions of oxidative stress. Said drugs can be used also in those pathologies wherein inflammation plays a significant pathogenetic role, such as for instance, but not limited to, in cancer, asthma, miocardic infarction.
- Adrenergic blockers, of α - or β -blocker type: the action spectrum of the compounds of formula (I) results wider than that of the starting drugs: to a direct action on the smooth musculature the inhibition of the nervous beta-adrenergic signals governing the contraction of the hematic ducts is associated. The side effects (dyspnoea, bronchoconstriction) affecting the respiratory apparatus are lower.
- Antithrombotic drugs: the antiplatelet activity is potentiated and in the case of the aspirin derivatives the gastric tolerability is improved.
- Bronchodilators and drugs active on the cholinergic system: the side effects affecting the cardio-vascular apparatus (tachycardia, hypertension) result lowered.
- Expectorants and mucolytic drugs: the gastrointestinal tolerability results improved.
- Diphosphonates: the toxicity relating to the gastrointestinal tract is drastically lowered.
- Phosphodiesterase (PDE) inhibitors (bronchodilators): the therapeutic efficacy is improved, the dosage being equal; it is therefore possible, using the compounds of the invention to administer a lower dose of the drug and reduce the side effects.
- Anti leukotrienic drugs: better efficacy.
- ACE inhibitors: better therapeutic efficacy and lower side effects (dyspnoea, cough) affecting the respiratory apparatus.
- Antidiabetic drugs (insulin-sensitizing and hypoglycaemizing), antibiotic, antiviral, antitumoral,

anticolinergic drugs, drugs for the dementia therapy: better efficacy and/or tolerability.

The drugs which can be used as precursors in the general formula of the compounds of the invention are all those meeting at least one of the above mentioned tests 1, 2, 3. Examples of precursor drugs which can be used are the following:

For anti-inflammatory/analgesic drugs, the following can for example be mentioned:

anti-inflammatory drugs: aceclofenac, acemetacin, acetylsalicylic acid, 5-amino-acetylsalicylic acid, alclofenac, alminoprofen, amfenac, bendazac, bermoprofen, α -bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen, cinmetacin, clidanac, clopirac, diclofenac sodium, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, oxaceprol, oxaprozin, oxyphenbutazone, parsalmide, perisoxal, phenyl acetylsalicylate, olsalazine, pyrazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicylamide O-acetic acid, salicylsulphuric acid, salsalate, sulindac, suprofen, suxibuzone, tenoxicam, tiaprofenic acid, tiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepirac, tomoxiprol; sulindac, differently from other antiinflammatory compounds FANS, is not a cox-inhibitor;

analgesic drugs: acetaminophen (paracetamol), acetaminosalol, aminochlorthenoxazin, acetylsalicylic 2-amino-4-picoline acid, acetylsalicylsalicylic acid, anileridine, benoxaprofen benzylmorphine, 5-bromosalicylic acetate acid, buccetin, buprenorphine, butorphanol, capsaicine, cinchophen, ciramadol, clometacin, clonixin, codeine, desomorphine, dezocine, dihydrocodeine, dihydromorphine, dimepheptanol, dipyrrocetyl, eptazocine, ethoxazene, ethylmorphine, eugenol, floctafenine, fosfosal, glafenine, hydrocodone, hydromorphone,

hydroxypethidine, ibufenac, p-lactophenetide, levorphanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nico-morphine, norlevorphanol, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, phenocoll, phenoperidine, phenyl-butazone, phenylsalicylate, phenylramidol, salicin, salicyl-amide, tiorphan, tramadol, diacerein, actarit;
paracetamol is not a cox-inhibitor;

for respiratory and urogenital apparatus drugs (bronchodilators and drugs active on the cholinergic system, expectorants/mucolytics, antiasthmatic/antiallergic antihistaminic drugs), the following can be mentioned:

bronchodilators and drugs active on the cholinergic system: acefylline, albuterol, bambuterol, bamifhylline, bevonium methyl sulphate, bitolterol, carbuterol, clenbuterol, chlorprenaline, dioxethedrine, difylline, ephedrine, epinephrine, eprozinol, etafredine, ethylnorepinephrine, etofylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium bromide, isoetharine, isoprotenerol, mabuterol, metaproterenol, oxybutynin, oxitropium bromide, pirbuterol, procaterol, protokylol, proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, 1-teobromineacetic acid, tiotropium bromide, tretoquinol, tulobuterol, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetrahydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: acetyl-cysteine, ambroxol, bromhexine, carbocysteine, domiodol, erdosteine, ferulic acid, guaiacol, guaifenesin, iodinated glycerol, letosteine, mecysteine hydrochloride, mesna, sobrerol, stepronin, terpin, tiopronin;

antiasthmatic/antiallergic antihistaminic drugs: acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam, chromoglycate, chromolyn, epinastine, fexofenadine, formoterol, histamine, hydroxyzine, levocabastine, lodoxamide, mabuterol, metron s, montelukast, nedocromil, repirinast, seratrodast, suplatast tosylate, terfenadine, tiaramide, urushiol, bromhexine;

for cardiovascular drugs (ACE-inhibitors, beta-blockers, antithrombotic and vasodilator drugs, antidiabetic and hypoglycemic drugs), the following can be mentioned:

ACE-inhibitors: alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, losartan, moveltipril, naphthopidil, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, urapidil;

beta-blockers: acebutolol, alprenolol, amosulalol, arotinolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, dilevalol, epanolol, esmolol, indenolol, labetalol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipridalol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol;

antithrombotic and vasoactive drugs: acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betahistine, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, dalteparin, dipyridamole, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, heparin, lamifiban, midrodine, nadroparin, nicotinyl alcohol, nylidrin, ozagrel, perhexiline, phenylpropanolamine, prenylamine, papaveroline, reviparin salt, ridogrel, suloctidil, tinofedrine, tinzaparin, trifusal, xanthinol niacinate;

antidiabetic drugs: acarbose, carbutamide, glibornuride glybuthiazol(e), miglitol, repaglinide, troglitazone, 1-butyl-3-metanyl-urea, tolrestat, nicotinamide;

for antitumoral drugs, the following can be mentioned: ancitabine, anthramycin, azacitidine, azaserine, 6-azauridine, bicalutamide, carubicin, carzinophilin, chlorambucil, chlorozotocin, cytarabine, daunorubicin, defosfamide, demecolcine, denopterin, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicin, droloxifene, edatrexate, eflornithine, enocitabine, epirubicin, epitiostanol, etanidazole, etoposide, fenretinide, fludarabine, fluorouracil, gemcitabine, hexestrol, idarubicin, lonidamine, mannomustine, melphalan, menogaril, 6-mercaptopurine, methotrexate, mitobronitol, mitolactol, mitomycins, mitoxantrone, mopidamol, mycophenolic acid, ninopterin, nogalamycin, paclitaxel, pentostatin, pira-

rubicin, piritrexim, plicamycin, podophyllic acid, porfimer sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, thiamiprine, thioguanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicin;

for antiulcer drugs the following can be mentioned: acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecabet, enprostil, esaprazole, irsogladine, misoprostol, omeprazole, ornoprostil, pantoprazole, plaunotol, rioprostil, rosaprostol, rotraxate, sofalcone, trimoprostil;

among anti-hyperlipidemic drugs (statines) the following can be mentioned: atorvastatin, cilastatin, dermostatin, fluvastatin, lovastatin, mevastatin, nystatin, pentostatin, pepstatin, privastatin sodium, simvastatin;

among antibiotic/antiviral drugs the following can be mentioned:

antibiotics: amdinocillin, amoxicillin, ampicillin, apalcillin, apicycline, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoylpas, benzyl penicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephaetrile sodium, cephalalexin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cephapirin sodium, cephradine, chloramphenicol, chlortetracycline, cinoxacin, clavulanic acid, clometocillin, cloxacillin, cyclacillin, cycloserine, demeclocycline, dicloxacillin, epicillin, fenbecillin, flomoxef, floxacillin, hetacillie, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, meclocycline, meropenem, metampicillin, methacycline, methicillin sodium, mezlocillin, minocycline, moxalactam, mupirocin, myxin, negamycin, novobiocin, oxacillin, panipenem, penicillin G potassium salt,

penicillin N, penicillin O, penicillin V, phenethicillin potassium salt, pipacycline, piperacillin, pirlimycin, porfirimycin, propicillin, quinacillin, ritipenem, rolitetracycline, sancycline, sedecamycine, spectinomycin, sulbactam, sulbenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidin, azithromycin, clarithromycin, dirithromycin, enviomycin, erythromycin, josamycin, midecamycin, miokamycin, oleandomycin, rifabutin, rifamide, rifamycin, rifaximin, rokitamycin, spiramycin, troleandomycin, viomycin, virginiamycin;

amikacin, apramycin, arbekacin, dibekacin, dihydrostreptomycin, fortimicins, gentamicin, micronomicin, neomycin, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin;

bacampicillin, cefcapene pivoxil, cefpodoxime proxetil, panipenem, pivampicillin, pivcefalexin, sultamicillin, talampicillin;

carbomycin, clindamycin, lincomycin, mikamycin, rosaramicin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, flumequine, grepafloxacin, lomefloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rufloxacin, sparfloxacin, tosufloxacin, trovafloxacin, clomocycline, guamecycline, oxytetracycline, nifurpirinol, nifurprazine; p-aminosalicylic acid, p-aminosalicylic acid hydrazide, clofazimine, deoxydihydrostreptomycin, ethambutol, glyconiazide, isoniazid, opiniazide, phenyl aminosalicylate, rifampin, rifapentine, salinazid, 4-4'-sulfynyldianiline, Acediasulfone, dapson, succisulfone, p-sulfanilylbenzylamine, thiazolsulfone, acetyl sulfamethoxypyrazine, mafenide, 4'-(methylsulfamoyl)sulfanilanilide, salazosulfadimidine, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 2-p-sulfanilylanilinoethanol, N⁴-sulfanilylsulfanilamide,

sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfisomidine, sulfisoxazole, 4-sulfanilamido salicylic acid; negamycin, carumonan, cloxyquin, nitroxoline, arginine, metronidazole;

antiviral drugs: acyclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, indanavir, kethoxal, lamivudine, MADU, penciclovir, podophyllotoxin, ribavirin, rimantadine, saquinavir, sorivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine;

among the bone resorption inhibitors (diphosphonates) the following can be mentioned: alendronic acid, butedronic acid, etidronic acid, oxidronic acid, pamidronic acid, risedronic acid;

among antidementia drugs the following can be mentioned: amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

The preferred substances are the following:

among anti-inflammatories: acetylsalicylic acid, 5-aminoacetylsalicylic acid, carprofen, diclofenac sodium, diflunisal, etodolac, flufenamic acid, flunixin, flurbiprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, naproxen, niflumic acid, olsalazine, piroxicam, salsalate, sulindac, suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, tolmetin, zomepirac, tomoxiprol;

among analgesic drugs: acetaminophen, acetylsalicylic acid, benoxaprofen, buprenorphine, butorphanol, capsaicin, diacerein, dihydrocodeine, ethylmorphine, eugenol, phenylbutazone, meptazinol, morphine, nalbuphine, pentazocine, thiorphan, tramadol, actarit;

among respiratory and urogenital apparatus drugs: (bronchodilators; drugs active on the cholinergic system, expectorants/mucolytics, antiasthmatics/antiallergic antihistaminic drugs):

bronchodilators and drugs active on the cholinergic system: albuterol, carbuterol, clenbuterol, diphylline, etophylline, fenoterol, ipratropium bromide, metaproterenol, oxybutynin, pirbuterol, salmeterol, terbutaline, tiotropium bromide, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetrahydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: acetyl-cysteine, ambroxol, bromexine, carbocysteine, guaiacol, ferulic acid, mecysteine hydrochloride, sobrerol;

antiasthmatic/antiallergic antihistaminic drugs: cetirizine, chromoglycate, histamine, levocabastine, lodoxamide, montelukast, terfenadine, bromhexine.

Among cardiovascular drugs:

ACE-inhibitors: captopril, enalapril, lisinopril, losartan, ramipril;

beta blockers: alprenolol, atenolol, bupranolol, labetalol, metipranolol, metoprolol, pindolol, propranolol, timolol;

antithrombotic and vasoactive drugs: acetylsalicylic acid, acetorphan, argatroban, clopidogrel, dalteparin, dipyridamole, enoxaparin, heparin, iloprost, midodrine, ozagrel, phenylpropanolamine trifusal;

antidiabetic drugs: tolrestat, nicotinamide;

among antitumoral drugs: anthramycin, daunorubicin, doxorubicin, epirubicin, fluorouracil, methotrexate, vinblastine;

among antiulcer drugs: cimetidine, omeprazole, pantoprazole;

among antihyperlipidemic drugs: lovastatin, pravastatin sodium, simvastatin;

Among antibiotic/antiviral drugs:

antibiotic drugs: amoxicillin, ampicillin, aztreonam, biapenem, carbenecillin, cefaclor, cefadroxil, cefamandole, cefatrizine, cefoxitin, clavulanic acid, dicloxacillin, imipenem, meclocycline, methacycline, moxalactam, panipenem, sulbactam, azithromycin, erythromycin, josamycin, miokamycin, rifabutine, rifamide, rifamycin, gentamicin, paromomycin, sisomicin, bacampicillin, carbomycin, clindamycin, ciprofloxacin, clinafloxacin, difloxacin, enrofloxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pipemidic

acid,

apicycline, clomocycline, oxytetracycline, nifurpirinol, nifurprazine, isoniazid, rifampin, rifapentine, dapsone, thiazolsulfone, sulfamethoxazole, sulfamoxole, metronidazole, arginine;

antiviral drugs: acyclovir, famciclovir, ganciclovir, penciclovir, ribavirin, vidarabine, zidovudine;

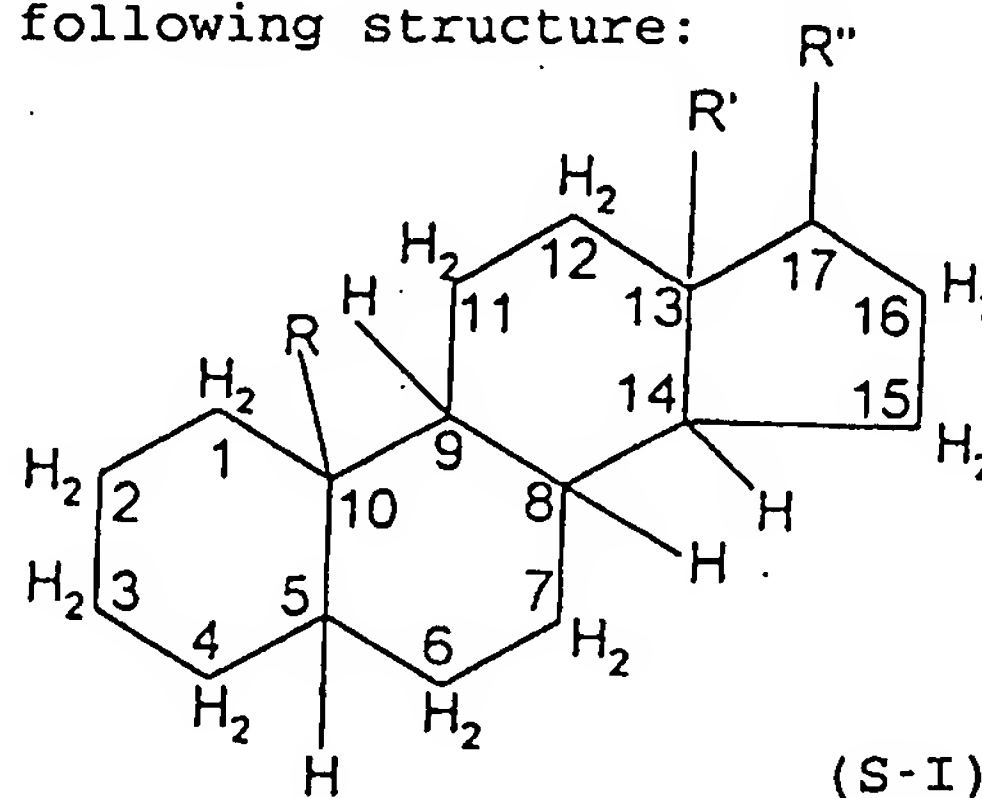
among the bone resorption inhibitors: alendronic acid, etidronic acid, pamidronic acid;

among antimentia drugs: oxiracetam, tacrine, velnacrine.

The above mentioned substances, R precursors, are prepared according to the methods known in the prior art. See for example in "The Merck Index, 12a Ed. (1996), herein incorporated by reference. When available, the corresponding isomers, comprising optical isomers, can be used.

Tomoxiprol is obtained according to the method described in EP 12,866.

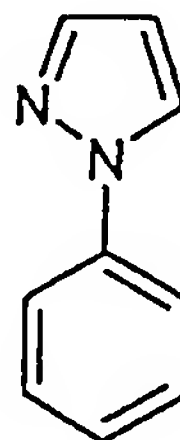
When in the compounds of formula (I) the precursor drug is a steroid, A = R- having the following structure:



wherein in substitution of the hydrogens of the CH groups or of the two hydrogens of the CH₂ groups mentioned in the general formula, the following substituents can be present:

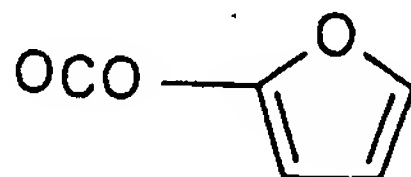
in position 1-2: there may be a double bond;

in position 2-3: there may be the following substituent:



(S-II)

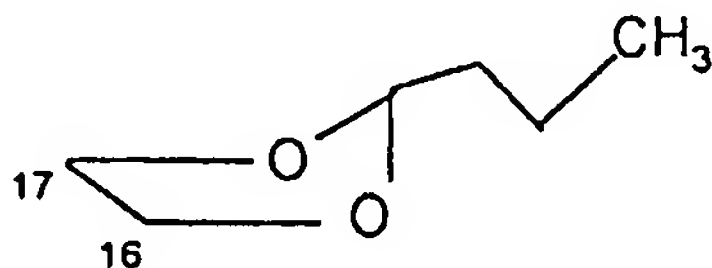
in position 2: there may be Cl, Br;
 in position 3: there may be CO, -O-CH₂-CH₂-Cl, OH;
 in position 3-4: there may be a double bond;
 in position 4-5: there may be a double bond;
 in position 5-6: there may be a double bond;
 in position 5-10: there may be a double bond;
 in position 6: there may be Cl, F, CH₃, -CHO;
 in position 7: there may be Cl, OH;
 in position 9: there may be Cl, F;
 in position 11: there may be OH, CO, Cl, CH₃;
 in position 16: there may be CH₃, OH, =CH₂;
 in position 17: there may be OH, CH₃, OCO(O)_{ua}(CH₂)_{va}CH₃, C≡CH
 or



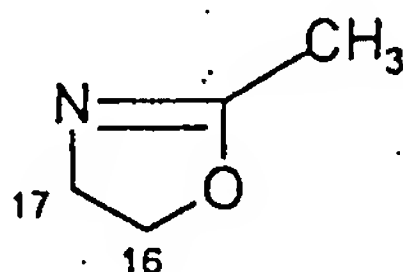
(S-III)

wherein ua is an integer equal to 0 or 1, va is an integer from 0 to 4;

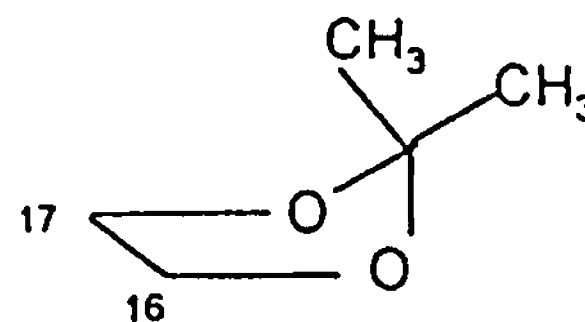
in position 16-17: there may be the following groups:



(S-IVa)



(S-IVb)



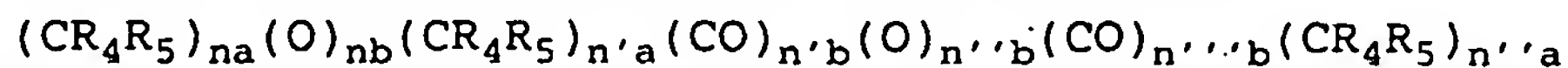
(S-IVc)

R and R', equal to or different from each other, can be hydrogen or linear or branched alkyls from 1 to 4 carbon atoms, preferably R = R' = CH₃;

R" is -(CO-L)_t-(L)_{t2}-(X₀^I)_{t1}-

wherein t, t1 and t2 are integers equal to or different from each other, equal to 0 or 1, with the proviso that when t = 0 t2 = 1 and when t = 1 t2 = 0, and that t and t1, or t2 and t1, cannot contemporaneously be equal to 0 when A does not contain -OH groups;

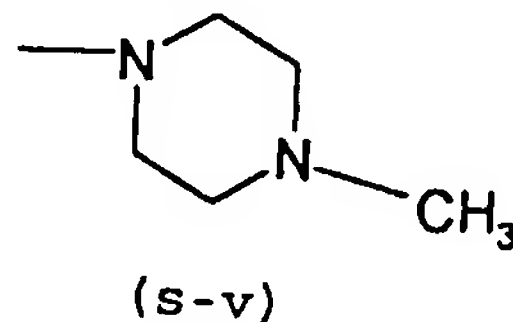
the bivalent bridging group L is selected from:



wherein na, n'a, and n''a, equal to or different from each other, are integers from 0 to 6, preferably 1-3; nb, n'b, n''b

and $n''b$, equal to or different from each other, are integers equal to 0 or 1; R_4 , R_5 , equal to or different from each other, are selected from H, linear or branched alkyl from 1 to 5 carbon atoms, preferably from 1 to 3;

X_0^I is X as above defined, or equal to X_2^I wherein X_2^I is equal to OH, CH_3 , Cl, $N(-CH_2-CH_3)_2$, SCH_2F , SH, or



Preferably R'' in the formula (S-I) is $-CO-CH_2OH$, or $CH(CH_3)-CH_2-CH_2-COOH$.

In the precursor steroids those having the hydroxyl function in position 3 and/or in position 11, and/or having in R'' an hydroxyl or carboxylic function in terminal position, are preferred.

The precursor steroids of A which can be mentioned and which are preferred, are those listed hereinunder, obtainable according to the processes known in the prior art.

As precursors and respective processes, those for example described in The Merck Index, ed. 12 of 1996, herein incorporated by reference, can be mentioned. The precursors (according to the Merck nomenclature) are the following, wherein H_2 , H, R, R' , R'' have the meaning mentioned in the compounds listed herein: Budesonide, Hydrocortisone, Alclomethasone, Algestone, Beclomethasone, Betamethasone, Chloroprednisone, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Cortisone, Corticosterone, Deflazacort, Desonide, Desoximethasone, Dexamethasone, Diflorasone Diflucortolone, Difluprednate, Fluazacort, Flucloronide, Flumethasone, Flunisolide, Fluocinolone Acetonide, Fluocinonide, Fluocortyn Butyl, Fluocortolone, Fluorometholone, Fluperolone Acetate, Fluprednidene Acetate, Fluprednisolone, Flurandrenolide, Formocortal, Halcinonide, Halobetasol Propionate, Halomethasone, Halopredone Acetate, Hydrocortamate, Loteprednol Etabonate, Medrysone, Meprednisone, Methylprednisolone, Momethasone Furoate, Paramethasone, Prednicarbate, Prednisolone, Prednisolone 25-Diethylaminoacetate, Prednisolone Sodium Phosphate, Prednisone, Prednival, Prednylidene, Rimexolone, Triamcinolone, Tri-

amcinolone Acetonide, 21-Acetoxypregnenolone, Cortivazol, Amcinonide, Fluticasone Propionate, Mazipredone, Tixocortol, Triamcinolone Hexacetonide, Ursodesoxycholic acid, Chenodeoxycholic acid, Mitatrienediol, Moxestrol, Ethynylestradiol, Estradiol, Mestranol.

The efficacy of the compounds according to the present invention as drugs to be used in the conditions of moderate oxidative stress has been shown also in a pharmacological test in which said compounds have been able to inhibit the cytolesive effects induced by hydrogen peroxide on human endothelial cells of the umbilical vein. The endothelial cell is one of the first cell hit in pathological processes ("Pathophysiology: the biological basis for disease in adults and children" by McCance & Huether, 1998, page 1025) and the hydrogen peroxide is a mild oxidant and is considered as an essential mediator agent in pathologies connected to oxidative stress (B. Halliwell, J. Gutteridge "Free Radicals in Biology and Medicine", page 416, 1993). The effectiveness to neutralize their cytolesive effects is considered essential for the pharmacological activity of compounds to be used under oxidative stress conditions (B. Halliwell, J. Gutteridge "Free Radicals in Biology and Medicine", page 416, 1993).

The compounds of formula (I) are prepared by means of the reactions specified below.

If the reactive function of the drug (for example -COOH, -OH) is involved in a covalent bond, for example of ester, amide, ether type, said function, before carrying out the preparation of the mentioned compounds, can be restored with the methods well known in the prior art.

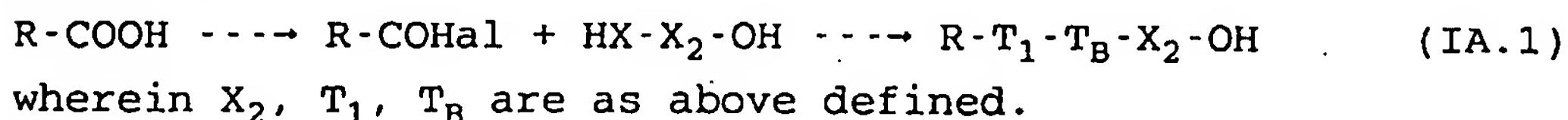
The reactions used for obtaining the compounds of formula (I) are reactions leading to the formation of bonds for example of ester, amide, thioester type well known to the skilled in the field.

When in the two reaction compounds other functional groups COOH and/or HX, wherein X is as above defined, are present, they must be protected before the reaction according to the methods known in the prior art; for example as described in the publication by Th. W. Greene: "Protective groups in organic synthesis", Harward University Press, 1980.

The compounds of formula I wherein $s = 2$ are prepared as mentioned hereinafter.

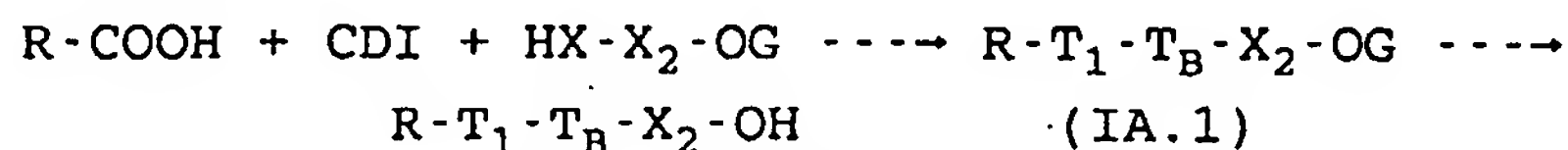
IA)- The drug has general formula $R\text{-COOH}$ and the functional group of the precursor compound of B which links itself to the drug carboxylic function has formula XZ , X being as above defined and $Z = H$, an OH function or an halogen atom being also contemporaneously present in the precursor compound of B as reactive groups for the nitration reaction.

The general synthesis scheme, if in the precursor compound of B also an OH function is present, implies the initial formation of the $R\text{-COHal}$ acid halide ($\text{Hal} = \text{Cl}, \text{Br}$) and the subsequent reaction with the HX group of the precursor compound of B:



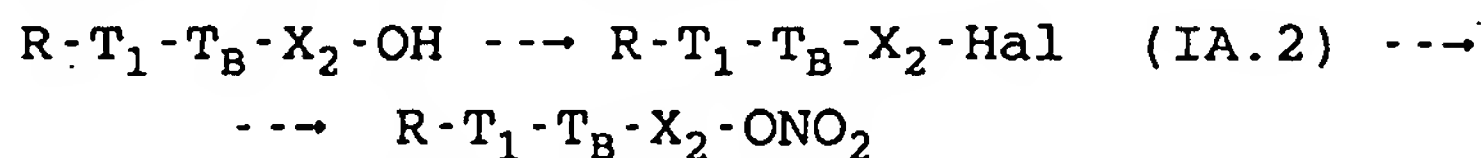
The RCOHal acylhalide is prepared according to the methods known in the prior art, for example by thionyl or oxalyl chloride, or by P^{III} or P^{V} halides in inert solvents under the reaction conditions, such as for example toluene, chloroform, DMF, etc. Then the acyl halide is reacted with the group HX of the precursor of B by using an inert solvent under the reaction conditions such as toluene, tetrahydrofuran, chloroform, etc. at a temperature in the range 0°C - 25°C .

Alternatively to the previous synthesis, the precursor drug of formula $R\text{-COOH}$ can be treated with an agent activating the carboxyl group selected from N,N' -carbonyldiimidazol (CDI), N,N' -dicyclohexylcarbodiimide in an inert solvent under the reaction conditions such as toluene, tetrahydrofuran, chloroform, etc. at a temperature in the range -5°C and $+50^\circ\text{C}$. The obtained compound is reacted in situ with the precursor of B, after the OH function present in the precursor of B has been protected, for example by formation of an acetyl group, recovering the initial function at the end of the synthesis by the methods well known in the prior art. The reaction scheme is the following:



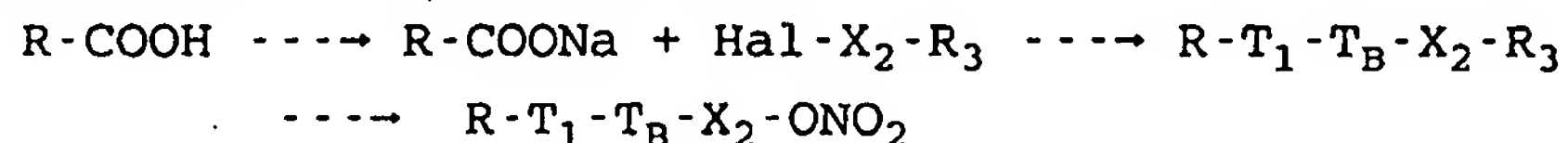
wherein X_2 , T_1 , T_B are as above defined and G is a protective group of the OH function.

The compound of formula (IA.1) is then subjected to halogenation reaction, for example by PBr_3 , PCl_5 , SOCl_2 , PPh_3 and I_2 in an inert solvent under the reaction conditions such as toluene, tetrahydrofuran, chloroform, etc. at a temperature in the range -5°C and $+50^\circ\text{C}$. The halogen derivative is reacted with AgNO_3 in organic solvent such as acetonitrile, tetrahydrofuran at a temperature in the range 25°C - 80°C . The reaction scheme is the following:



Alternatively, when X_2 is a linear C_4 alkyl, the R-COOH acid is reacted with triphenylphosphine in the presence of an halogenating agent such as CBr_4 or $\text{N-bromosuccinimide}$ in tetrahydrofuran and the resulting compound (IA.2), wherein X_2 is butylene, is nitrated as above mentioned.

Or it is possible to convert the R-COOH acid into its sodic salt, by using methods known in the prior art, and reacting it with an halogen derivative of formula $\text{Hal-X}_2\text{-R}_3$ wherein R_3 is OH , Hal in an inert solvent under the reaction conditions such as tetrahydrofuran, chloroform, etc. at a temperature in the range -5°C and $+25^\circ\text{C}$. If $\text{R}_3=\text{Hal}$ the obtained derivative is nitrated as above mentioned. The reaction scheme is the following:



IIA) - The drug has general formula R-XH and the functional group of the precursor compound of B which links itself to the function HX of the drug is a carboxylic group, X being as above defined, an OH function or an halogen atom being also contemporaneously present in the precursor compound of B as reactive groups for the nitration reaction.

The general synthesis scheme implies the reaction of the acid $\text{HOOC-X}_2\text{-R}_4$ wherein R_4 is Hal , OG wherein G is a suitable protecting group, with an activating agent as mentioned in IA) and the subsequent reaction with the HX group of the drug.



wherein X_2 , T_1 , T_B , R_4 are as above defined.

The obtained compound (IIA.1) is transformed into the corresponding nitroderivative as mentioned in IA). If the

substituent OG is present, the protecting group is first removed by the known methods.

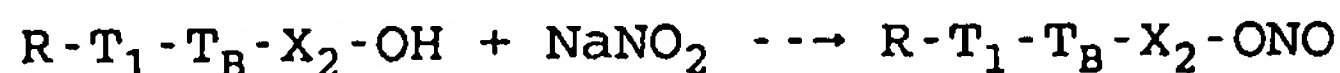
Alternatively to the previous synthesis, the drug R-OH is reacted with an acyl halide having formula Hal-X₂-COHal according to the conditions mentioned in IA) and the obtained halogen derivative is then nitrated as above mentioned:

$\text{HalOC-X}_2\text{-Hal} + \text{HX-R} \longrightarrow \text{R-T}_1\text{-T}_B\text{-X}_2\text{-Hal} \longrightarrow \text{R-T}_1\text{-T}_B\text{-X}_2\text{-ONO}_2$
wherein X₂, T₁, T_B are as above defined.

The compounds of formula I wherein s = 1 are prepared as mentioned hereinafter.

IB) - The drug has general formula R-COOH and the functional group of the precursor compound of B which links itself to the drug carboxylic function has formula XZ, X being as above defined and Z = H, the precursor compound of B containing also an hydroxyl function or an halogen atom as reactive groups for the nitration reaction.

The compound of formula R-T₁-T_B-X₂-OH (IA.1) obtained as reported in IA) is transformed into nitroso derivative by reaction with sodium nitrite in water in the presence of hydrochloric acid, according to the procedures known in the prior art.



IIB) - The drug has general formula R-XH and the functional group of the precursor compound of B which links itself to the function HX of the drug is a carboxylic group, X being as above defined. The synthesis scheme is similar to that described in IIA).

The compound of formula R-T₁-T_B-X₂-R₄ (IIA.1), obtained as reported in IIA) is transformed into the nitroso derivative as mentioned in IB).

The compounds of the present invention are formulated in the corresponding pharmaceutical compositions for parenteral, oral and topic use according to the methods well known in the prior art, together with the usual excipients; see for example the publication "Remington's Pharmaceutical Sciences 15a Ed."

The amount on molar basis of the active principle in these formulations is the same, or lower, in comparison with that used of the corresponding precursor drug.

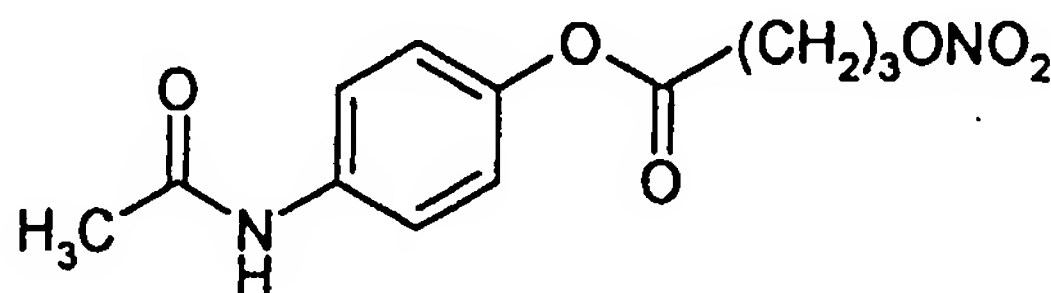
The daily administrable doses are those of precursor

drugs, or in the case lower. The daily doses can be found in the publications of the field, such as for example in "Physician's Desk reference".

The following examples have the purpose to illustrate the invention and are not to be considered as limitative of the same.

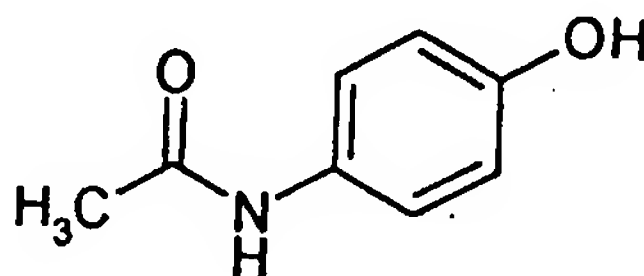
EXAMPLE 1

Preparation of 4-nitroxybutyric acid 4'-acetylamino phenyl ester



(E-1)

The drug is paracetamol of formula



(E-1a)

The precursor compound of B is the 4-hydroxybutyric acid.

a) Preparation of 4-bromobutyric acid 4'-acetylamino phenyl ester

To a solution of 4-bromobutyric acid (4.6 g, 27.6 mmol) in chloroform (45 ml) and N,N-dimethylformamide (20 ml), paracetamol (4.17 g, 27.6 mmol), N,N'-dicyclohexyl carbodiimide (8.42 g, 40.8 mmol) and 4-dimethyl aminopyridine (0.15 g, 1.25 mmol) are added. The reaction mixture is maintained under stirring at room temperature for 72 hours, filtered and evaporated under vacuum. The reaction crude material is treated with ethyl acetate and washed with brine and then with water. The organic phase is anhydriified with sodium sulphate and then evaporated under vacuum.

The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 4/6 (ratio V/V). 5.33 g of the

product are obtained as a white solid. M.p. = 108° - 110°C.

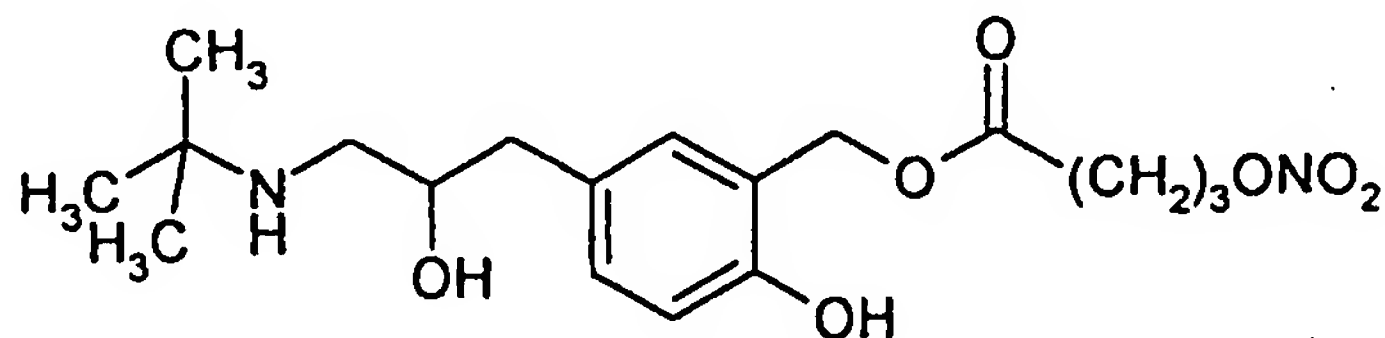
b) Preparation of 4-nitroxybutyric acid 4'-acetylamino phenylester

To a solution of 4-bromobutyric acid 4'-acetyl amino phenyl ester (5.33 g, 17.8 mmoles) in acetonitrile (80 ml) silver nitrate (4.56 g, 26.9 mmoles) is added. The reaction mixture is heated for 16 hours away from light at 80°C, then cooled to room temperature, filtered to remove the silver salts, and evaporated under reduced pressure. The residue is purged by chromatography on silica gel eluting with n-hexane/ethyl acetate 4/6. 4.1 g of the product are obtained as a white solid. M.P.= 80-83°C.

Elementary analysis:	C	H	N
Calculated	51.07%	4.99%	9.92%
Found	51.06%	5.00%	9.90%

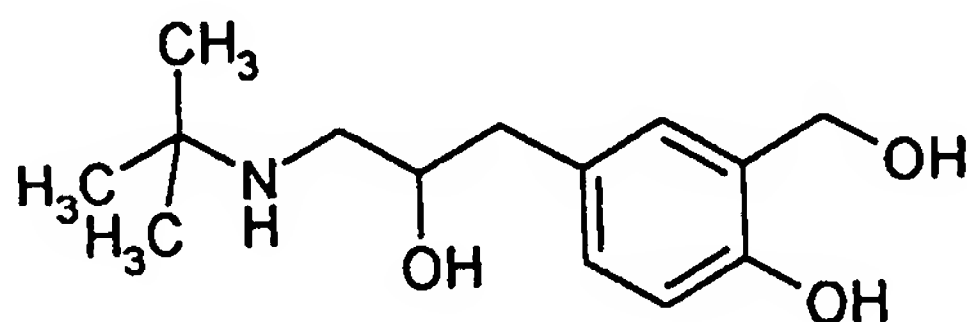
EXAMPLE 2

Preparation of 4-hydroxy-3-(4-nitroxybutanoyloxymethyl)- α -[[(tertbutylamino)methyl]benzyl alcohol



(E-2)

The precursor drug is salbutamol of formula



(E-2a)

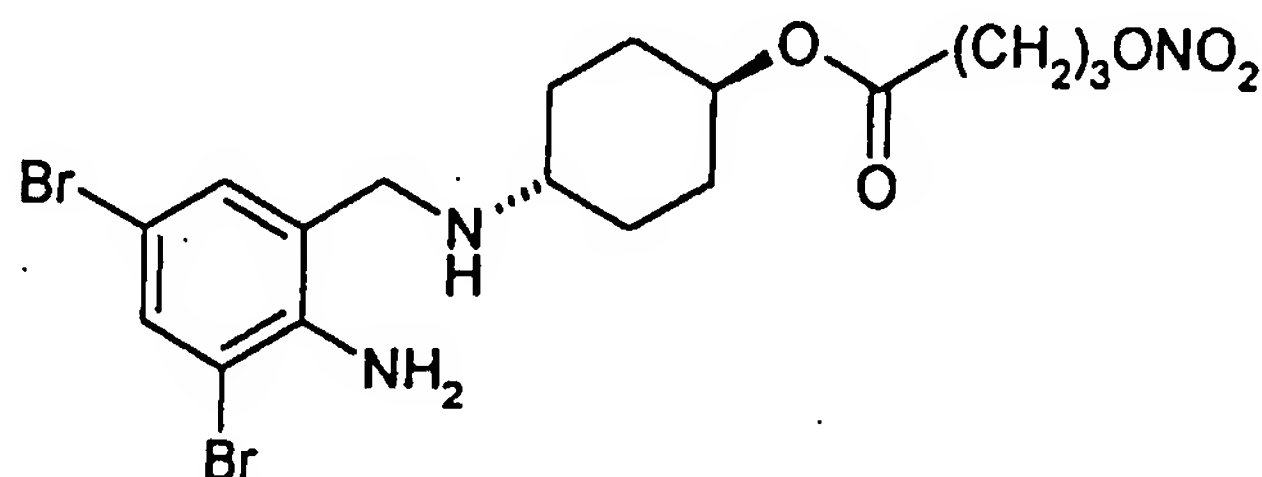
The precursor compound of B is the 4-hydroxybutyric acid.

The compound (E-2) is synthesized according to the procedure described in Example 1. Yield: 21%.

Elementary analysis:	C	H	N
Calculated	55.13%	7.07%	7.56%
Found	55.10%	7.09%	7.57%.

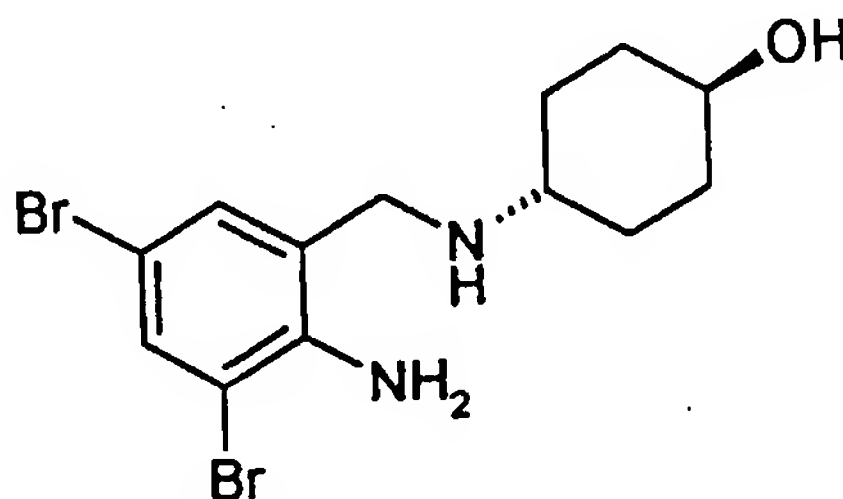
EXAMPLE 3

Preparation of 4-(nitroxy)butyric acid 4-[(2-amino-3,5-dibromophenyl) methylamino] trans cyclohexyl ester



(E-3)

The precursor drug is ambroxol



(E-3a)

The precursor compound of A is the 4-hydroxybutyric acid.

a) Preparation of 4-[(2-tert-butoxycarbonylamino-3,5-dibromophenyl) methylamino] trans cyclohexanol

To a solution of ambroxol (5 g, 13.22 mmoles) in dioxane (35 ml) and water (50 ml), triethylamine (3.31 ml, 23.7 mmoles) and di-tert-butylidicarbonate (3.46 g, 15.86 mmoles) are added. The reaction mixture is left under stirring at room temperature for 24 hours, then concentrated at reduced pressure. The residue is treated by adding portions of a 1% HCl solution until pH 7, then the solution is extracted with ethyl acetate. The organic phase anhydriified with sodium sulphate is evaporated under vacuum. 4-[(2-tert-butoxycarbonylamino-3,5-dibromophenyl)methylamino] trans cyclohexanol is obtained, which is used in the subsequent step without further

purification.

b) Preparation of 4-(nitroxy)butyric acid 4-[(2-tert-butoxycarbonylamino-3,5-dibromophenyl) methylamino] trans cyclohexyl ester

The compound is synthesized according to the procedure described in Example 1. Yield 57%.

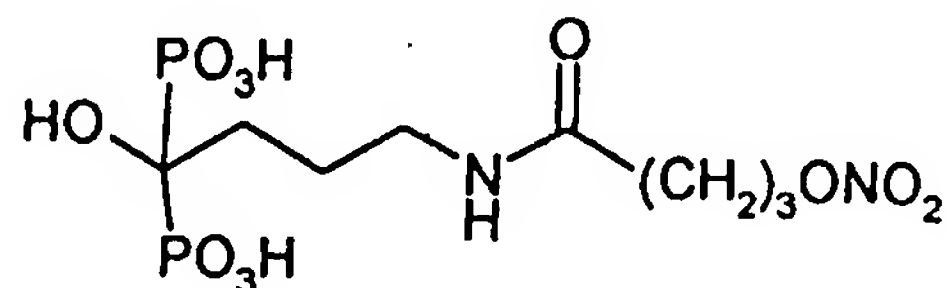
c) Preparation of 4-(nitroxy)butyric acid 4-[(2-amino-3,5-dibromophenyl) methylamino] trans cyclohexyl ester

To a solution of 4-(nitroxy)butyric acid 4-[(2-tert-butoxycarbonylamino-3,5-dibromophenyl) methylamino] trans cyclohexyl ester (3.5 g, 5.74 mmol) in ethyl acetate (100 ml), cooled at 0°C, a 5N HCl solution in ethyl acetate (5.95 ml) is added. The solution is maintained under stirring at 0°C for 5 hours, then filtered. The obtained solid is suspended in ethyl acetate and the organic layer washed with a 5% sodium carbonate solution. The organic phase is washed with water, anhydriified with sodium sulphate and evaporated at reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 1/1 (ratio by volume). 4-(nitroxy)butyric acid 4-[(2-amino-3,5-dibromophenyl) methylamino] trans cyclohexyl ester is obtained. Yield 31%.

Elementary analysis:	C	H	N	Br
Calculated	40.10%	4.55%	8.25%	31.38
Found	40.07%	4.54%	8.26%	31.39%

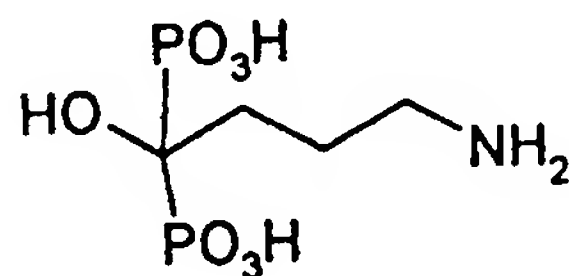
EXAMPLE 4

Preparation of [4-[4-(nitroxy)butyroyl]amino-1-hydroxybutylidene]biphosphonic acid



(E-4)

The precursor drug is alendronic acid of formula



(E-4a)

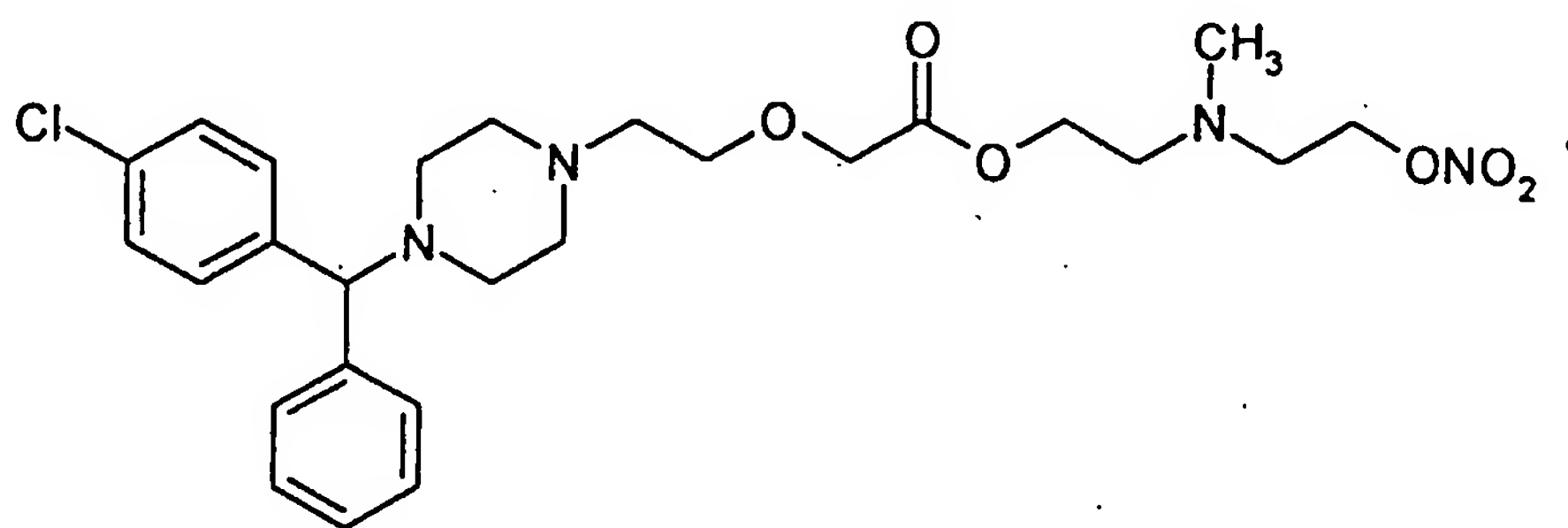
The precursor compound of B is 4-hydroxybutyric acid.

The compound is synthesized according to the procedure described in Example 1. Yield: 11%.

Elementary analysis:	C	H	N
Calculated	25.27%	4.77%	7.37%
Found	25.26%	4.79%	7.37%.

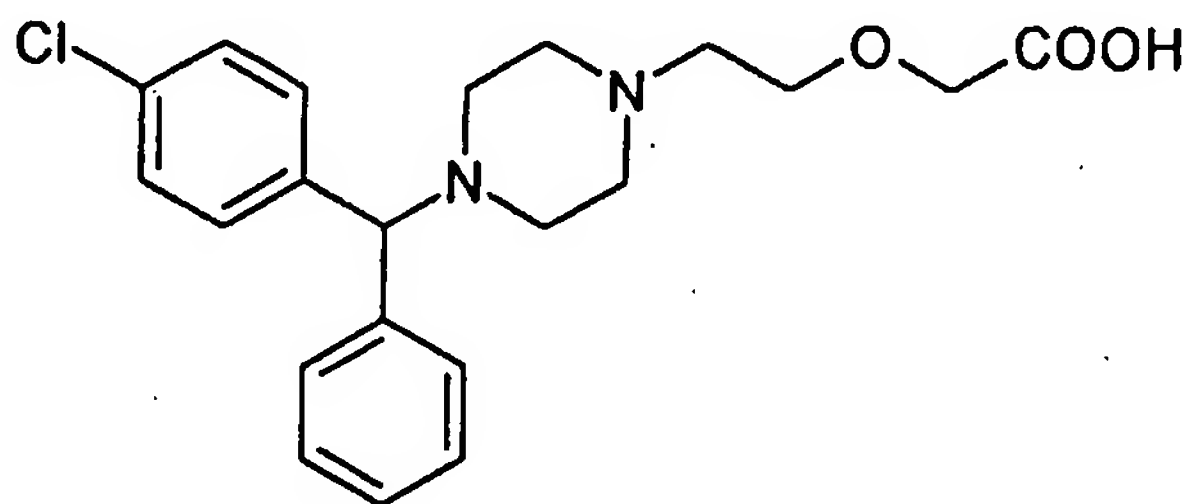
EXAMPLE 5

Preparation of [2-[4-[(4-chlorophenyl)phenylmethyl]1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-nitroxyethyl)]-2-aminoethyl ester



(E-5)

The precursor drug is cetirizine



(E-5a)

The precursor compound of B is N-methyldiethanolamine of formula $\text{HO}-(\text{CH}_2)_2-\text{N}(\text{CH}_3)-(\text{CH}_2)_2-\text{OH}$.

a) Preparation of [2-[4-[(4-chlorophenyl)phenylmethyl]1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-hydroxyethyl)]-2-aminoethyl ester

To a solution of cetirizine (5 g, 12.85 mmol) in N,N-dimethylformamide (5 ml) and toluene (50 ml), cooled at 0°C, oxalyl chloride (1.1 ml, 25.7 mmol) is slowly added. After

having maintained the reaction mixture under stirring for 12 hours at room temperature, it is evaporated under vacuum. To the obtained crude product, dissolved in tetrahydrofuran (40 ml) N-methyl diethanolamine (4.05 g, 38.55 mmoles) is added and the obtained solution is maintained under stirring at room temperature for 6 hours. The reaction mixture is evaporated at reduced pressure. The residue is treated with ethyl acetate and washed with water. The organic phase is anhydriified with sodium sulphate and dried. The crude product is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 3/7 (ratio by volume). [2-[4-[(4-chlorophenyl)phenylmethyl] 1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-hydroxyethyl)]-2-aminoethyl ester is obtained.

b) Preparation of [2-[4-[(4-chlorophenyl)phenylmethyl] 1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-chloroethyl)]-2-aminoethyl ester

To a solution of [2-[4-[(4-chlorophenyl)phenylmethyl] 1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-hydroxyethyl)]-2-aminoethyl ester (3.8 g, 7.75 mmoles) in chloroform (70 ml), cooled at 0°C, thionyl chloride (0.58 ml, 8.06 mmoles) in chloroform (30 ml) is added. The solution is left at 0°C for 30 minutes under stirring and then heated at 40°C for 6 hours. The reaction is then washed with a saturated sodium bicarbonate solution and subsequently with water. The organic phase, anhydriified with sodium sulphate, is evaporated at reduced pressure. The crude product is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 7/3 (ratio by volume). [2-[4-[(4-chlorophenyl)phenylmethyl] 1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-chloroethyl)]-2-aminoethyl ester is obtained.

c) Preparation of [2-[4-[(4-chlorophenyl)phenylmethyl] 1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-nitroxyethyl)]-2-aminoethyl ester

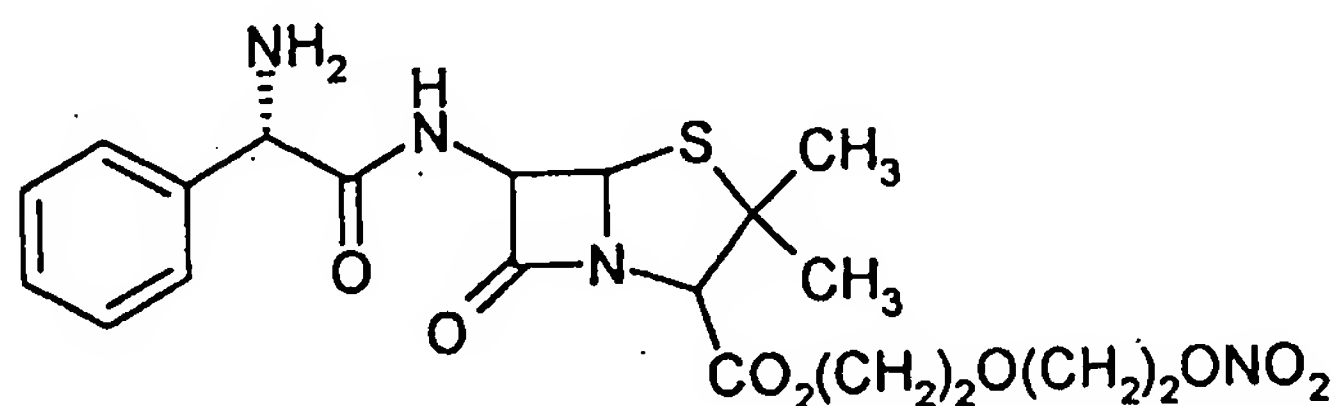
To a solution of [2-[4-[(4-chlorophenyl)phenyl methyl] 1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-chloroethyl)]-2-aminoethyl ester (2.3 g, 4.52 mmoles) in acetonitrile (100 ml), silver nitrate (1.53 g, 9.04 mmoles) is added. The reaction mixture is heated to 80°C away from light for 48 hours, then brought again to room temperature, filtered to remove the

silver salts and evaporated at reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 7/3 (ratio by volume). [2-[4-[(4-chlorophenyl)phenylmethyl]1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-nitroxyethyl)]-2-aminoethyl ester is obtained. Yield: 23%.

Elementary analysis:	C	H	N	Cl
Calculated	58.37%	6.59%	10.47%	6.63%
Found	58.38%	6.58%	10.45%	6.60%

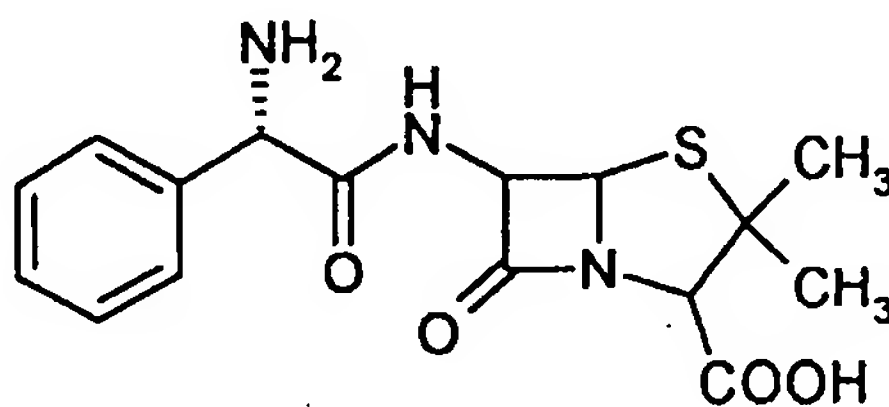
EXAMPLE 6

Preparation of 6-[D(-)- α -aminophenyl acetamido] penicillanic acid 5-(nitroxy)ethyloxyethyl ester



(E-6)

The precursor drug is ampicilline of formula



(E-6a)

The precursor compound of B is diethylenglycol.

a) Preparation of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid

To a solution of ampicilline (3 g, 8.58 mmoles) in a dioxane (18 ml) and water (25 ml) mixture, triethylamine (2.1 ml, 15.3 mmoles) and di-tert-butyl dicarbonate (2.24 g, 10.29 mmoles) are added. The reaction mixture is left under stirring at room temperature for 24 hours, then concentrated at reduced pressure. The residue is treated by subsequent additions of a 1% HCl solution until the pH of the aqueous phase is equal to

7. One extracts with ethyl acetate. The organic phase is anhydrified with sodium sulphate and then evaporated under vacuum. 6-[D(-)- α -tert butoxycarbonylamino phenyl acetamido] penicillanic acid is obtained, which is used in the subsequent synthesis step without further purging.

b) Preparation of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(hydroxy)ethyloxyethyl ester

To a solution of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid (3.8 g, 8.58 mmol) in a mixture of N,N-dimethylformamide (5 ml) and toluene (40 ml), cooled at 0°C, oxalyl chloride (0.74 ml, 17.16 mmol) is slowly added. The solution is left under stirring for 12 hours at room temperature and then evaporated under vacuum. The obtained crude product is dissolved in tetrahydrofuran (70 ml) and additioned with ethylenglycol (2.45 ml, 25.7 mmol). The obtained solution is maintained under stirring at room temperature for 5 hours and then evaporated at reduced pressure. The residue is treated with ethyl acetate and washed with water. The organic phase, anhydrified with sodium sulphate, is dried. The crude product is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 2/8 (ratio by volume). 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(hydroxy)ethyloxyethyl ester is obtained.

c) Preparation of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(chloro)ethyloxyethyl ester

To a solution of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(hydroxy)ethyloxy ethyl ester (3 g, 5.58 mmol) in chloroform (70 ml), cooled at 0°C, thionyl chloride (0.42 ml, 5.8 mmol) in chloroform (30 ml) is added. The solution is maintained under stirring at 0°C for 30 minutes and then heated at 40°C for 4 hours. Subsequently the mixture is washed with a saturated sodium bicarbonate solution and then with water. The organic phase is anhydrified with sodium sulphate and then evaporated at reduced pressure. The crude product is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 1/1 (ratio by volume). 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(chloro)ethyloxyethyl ester is obtained.

d) Preparation of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(nitroxy)ethyloxyethyl ester

To a solution of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(chloro)ethyloxyethyl ester (2.1 g, 3.77 mmol) in acetonitrile (100 ml), silver nitrate (1.28 g, 7.54 mmol) is added. The reaction mixture is heated at 80°C for 24 hours away from light. It is cooled at room temperature, filtered to remove the silver salts and evaporated at reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 1/1 (ratio by volume). 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(nitroxy)ethyloxyethyl ester is obtained.

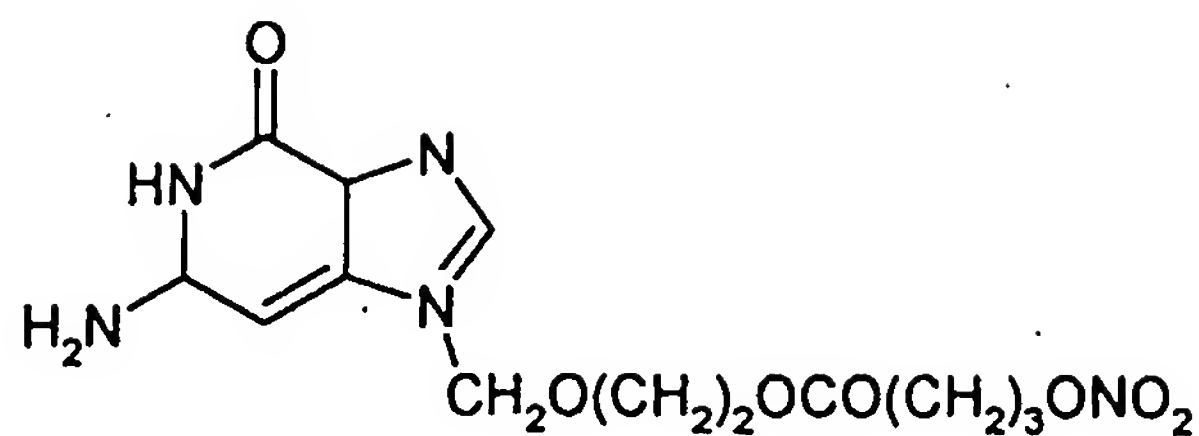
e) Preparation of 6-[D(-)- α -aminophenyl acetamido] penicillanic acid 5-(nitroxy)ethyloxyethyl ester

To a solution of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(nitroxy)ethyloxy ethyl ester (1.5 g, 2.57 mmol) in ethyl acetate (100 ml), cooled at 0°C, a 5N HCl solution in ethyl acetate (2.67 ml) is added. The solution is maintained at 0°C under stirring for 7 hours and then filtered. The obtained solid is suspended in ethyl acetate and washed with a 5% w/v sodium carbonate solution. The organic phase is washed with water, anhydriified with sodium sulphate and evaporated at reduced pressure. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 1/1 (ratio by volume). 6-[D(-)- α -amino phenyl acetamido] penicillanic acid 5-(nitroxy)ethyl oxyethyl ester is obtained. Yield: 13%.

Elementary analysis:	C	H	N	S
Calculated	49.79%	5.43%	11.61%	6.64%
Found	49.77%	5.45%	11.60%	6.65%

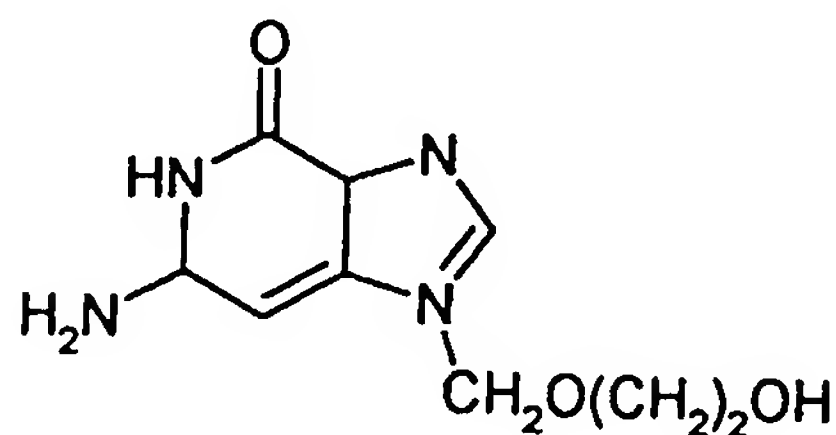
EXAMPLE 7

Preparation of 2-amino-1,9-dihydro-9-[[2-(4-nitroxybutyroyloxy)ethoxy)methyl]-6H-purin-6-one



(E-7)

The precursor drug is aciclovir of formula



(E-7a)

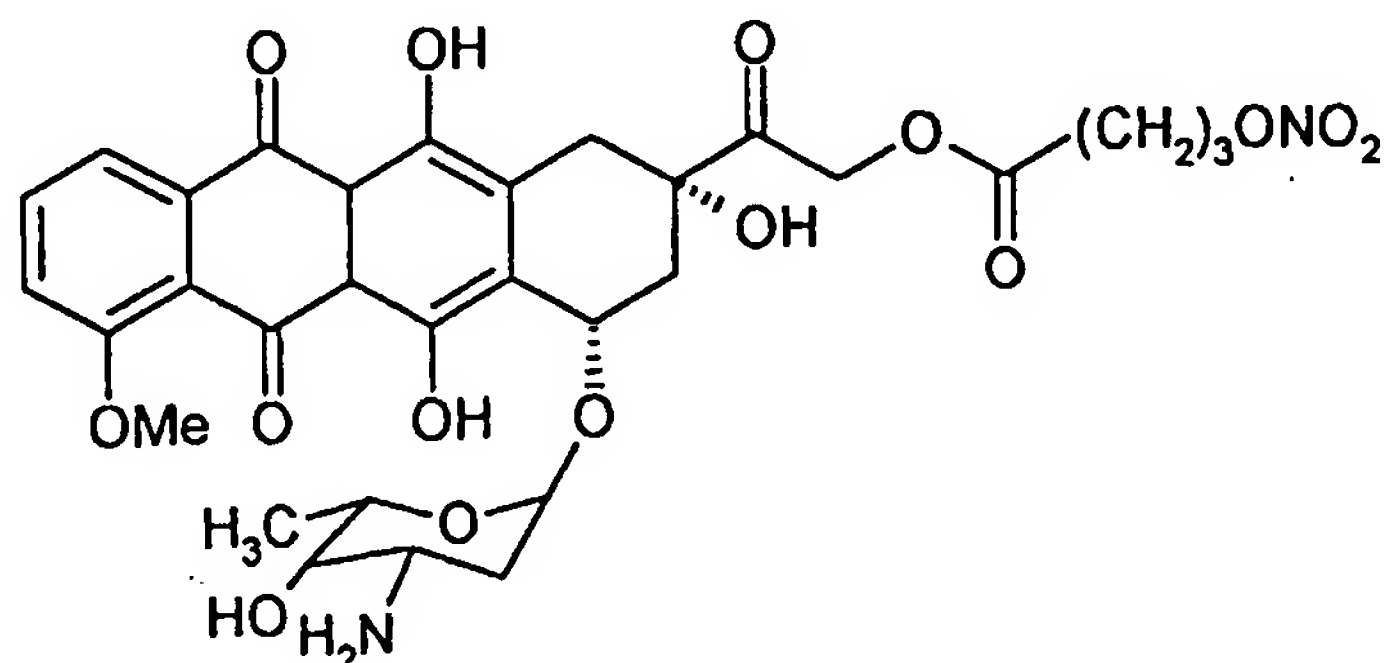
The precursor compound of A is the 4-hydroxybutyric acid.

The compound (E-6) is synthesized according to the procedure described in Example 3. Yield: 14%.

Elementary analysis:	C	H	N
Calculated	42.36%	4.74%	24.70%
Found	42.38%	4.77%	24.68%.

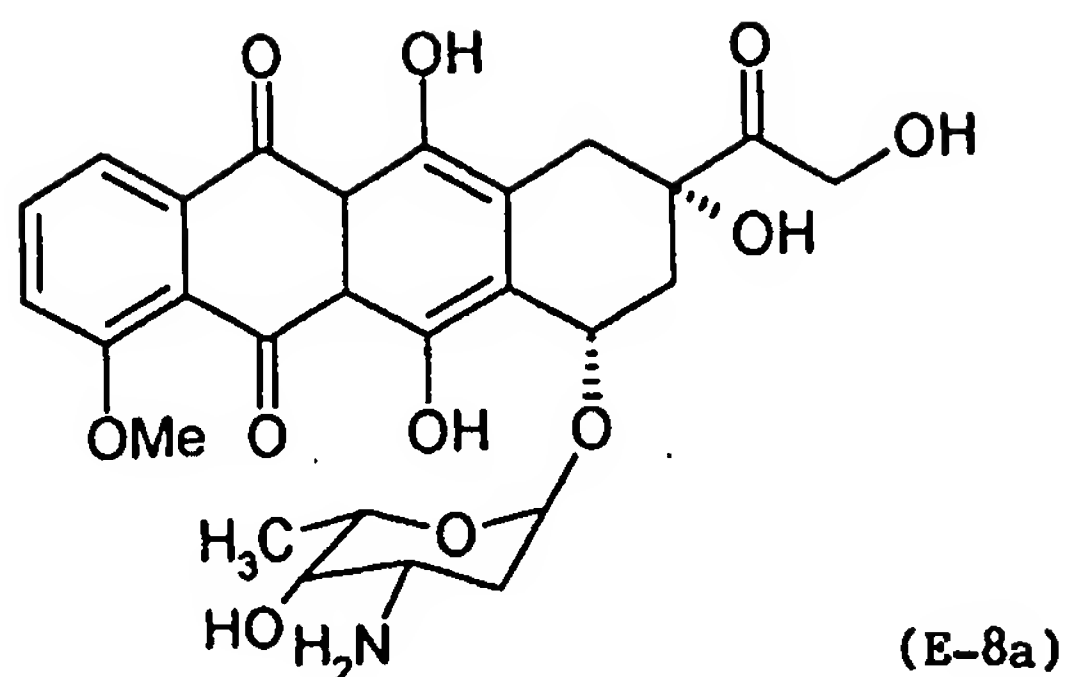
EXAMPLE 8

Preparation of (8S-cis)-10-[(3-amino-2,3,6-trideoxy- α -L-lixo-
hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-[(4-
nitroxybutyroyloxy)acetyl]-1-methoxy-5,12-naphthacendione



(E-8)

The precursor drug is doxorubicin of formula (E-8a)



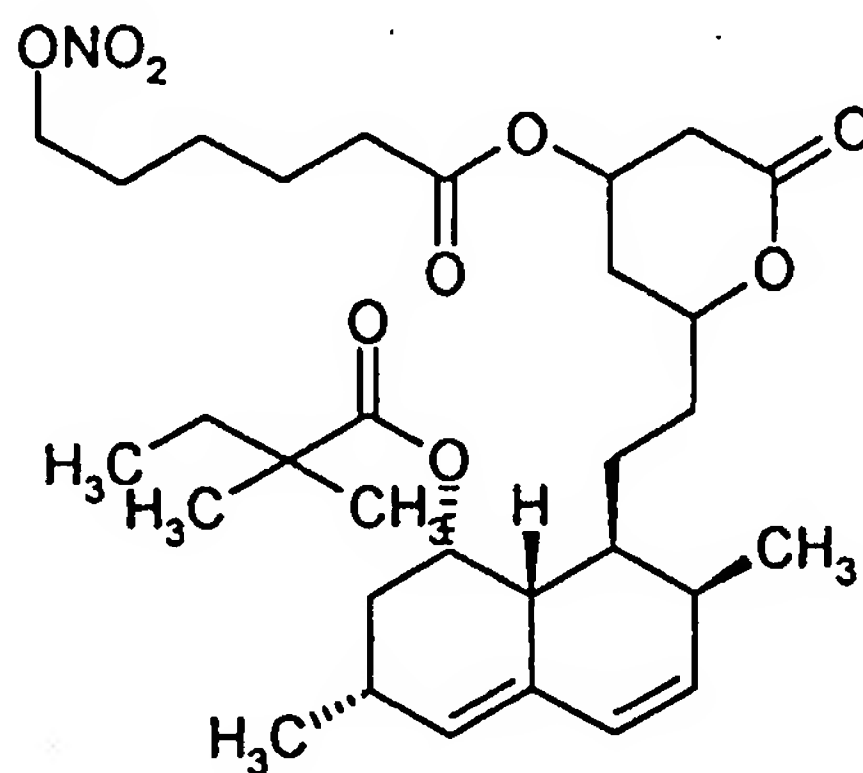
The precursor compound of B is the 4-hydroxybutyric acid.

The compound is synthesized according to the procedure described in Example 1. Yield: 7%.

Elementary analysis:	C	H	N
Calculated	56.53%	5.20%	4.25%
Found	56.55%	5.22%	4.23%.

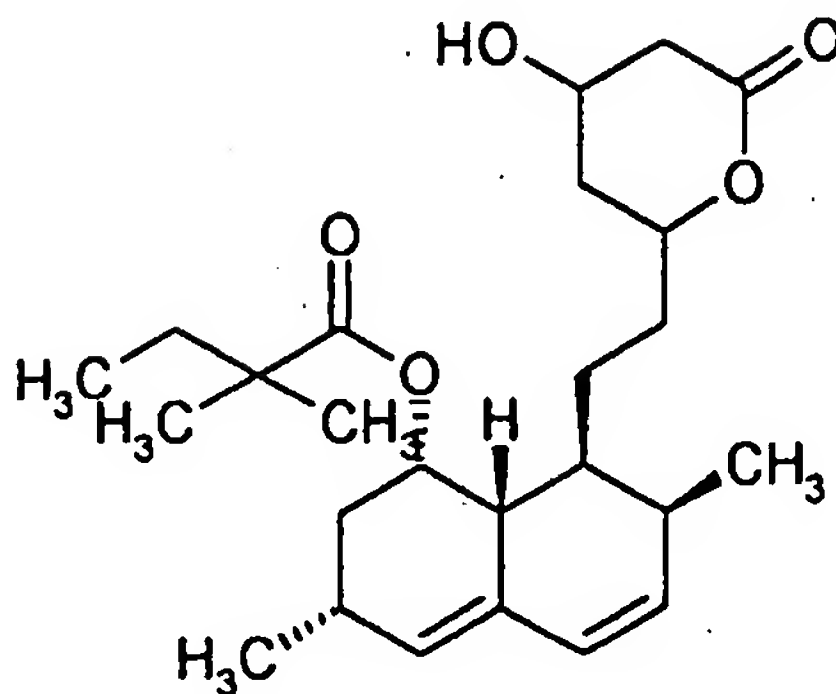
EXAMPLE 9

Preparation of di[1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 $\alpha\beta$]] 2,2-dimethyl butyric acid 1,2,3,7,8,8 α -hexahydro-3,7-dimethyl-8-[2-[tetrahydro-4-(6-nitroxyhexanoyloxy)-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester



(E-9)

The precursor drug is simvastatine of formula



(E-9a)

The precursor of the bridging bond B is 6-hydroxyhexanoic acid.

a) Preparation of [1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 $\alpha\beta$]] 2-2-dimethyl butyric acid 1,2,3,7,8,8 α -hexahydro-3,7-dimethyl-8-[2-[tetrahydro-4-(6-bromohexanoyloxy)-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester

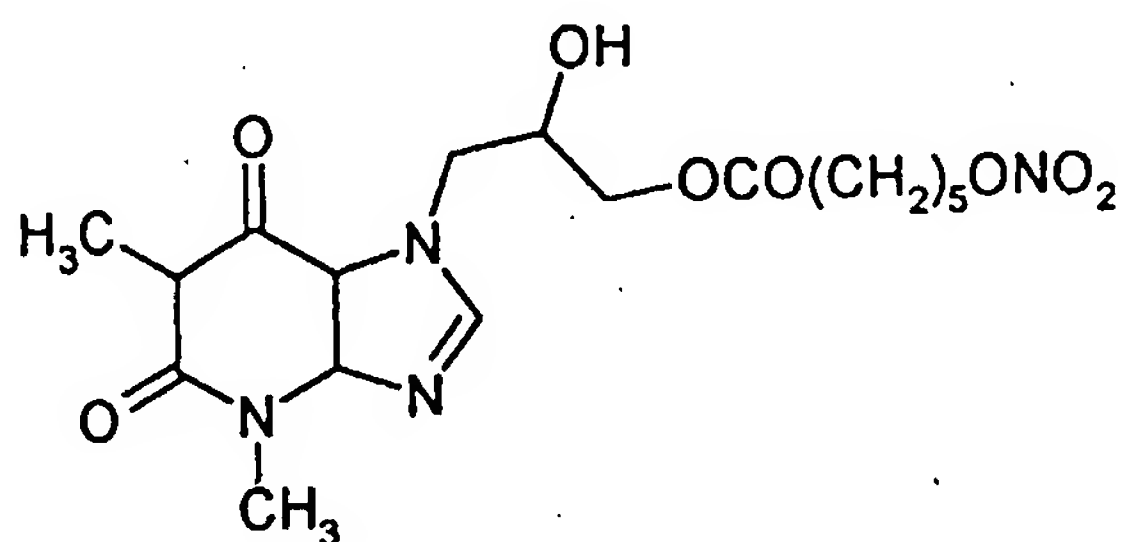
To a solution of simvastatine (4 g, 9.56 mmol) in chloroform (50 ml) and N,N-dimethylformamide (20 ml), 6-bromocaproic acid (1.86 g, 9.56 mmol), N,N'-dicyclohexylcarbodiimide (1.97 g, 9.56 mmol) and 4-dimethyl amino pyridine (52 mg, 0.43 mmol) are added. The reaction mixture is maintained under stirring at room temperature for 24 hours, then diluted with chloroform and washed with water. The organic phase, anhydriified with sodium sulphate, is evaporated at reduced pressure. The crude product is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 1/1 (ratio by volume). [1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 $\alpha\beta$]] 2-2-dimethyl butyric acid 1,2,3,7,8,8 α -hexahydro-3,7-dimethyl-8-[2-[tetrahydro-4-(6-bromohexanoyloxy)-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester is obtained.

b) Preparation of [1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 $\alpha\beta$]] 2-2-dimethyl butyric acid 1,2,3,7,8,8 α -hexahydro-3,7-dimethyl-8-[2-[tetrahydro-4-(6-nitroxyhexanoyloxy)-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester

To a solution of [1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 $\alpha\beta$]] 2-2-dimethyl butyric acid 1,2,3,7,8,8 α -hexahydro-3,7-dimethyl-8-[2-[tetrahydro-4-(6-bromohexanoyloxy)-6-oxo-2H-pyran-2-yl]ethyl]-

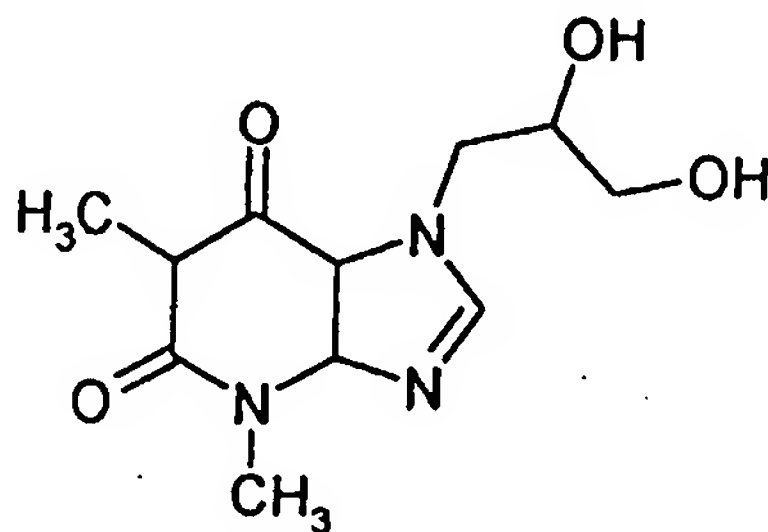
1-naphthalenyl ester (1 g, 1.67 mmol) in acetonitrile (60 ml) silver nitrate (0.57 g, 3.35 mmol) is added. The reaction mixture is heated for 6 hours at 80°C away from light, then it is cooled to room temperature, filtered to remove the silver salts and the organic phase is evaporated under reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 1/1 (ratio by volume). [1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 $\alpha\beta$]] 2,2-dimethyl butyric acid 1,2,3,7,8,8 α -hexahydro-3,7-dimethyl-8-[2-[tetrahydro-4-(6-nitroxyhexanoyloxy)-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester is obtained. Yield: 13%.

Elementary analysis:	C	H	N
Calculated	62.71%	7.97%	2.35%
Found	62.74%	7.99%	2.33%

EXAMPLE 10Preparation of 6-(nitroxy)hexanoic acid theophylline ester

(E-10)

The precursor drug is diphylline of formula:



(E-10a)

The precursor compound of B is the 6-hydroxyhexanoic acid.

The compound of formula (E-10) is synthesized according to the procedure described in Example 9. Yield: 23%.

Elementary analysis:	C	H	N
Calculated	44.76%	5.39%	16.31%
Found	44.77%	5.41%	16.33%.

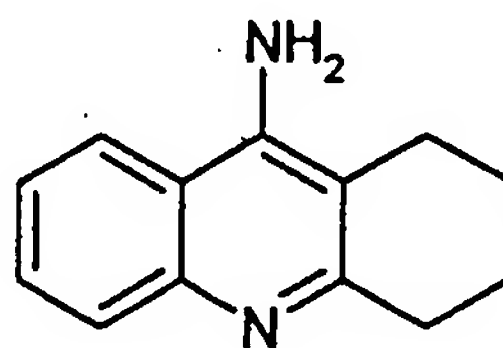
EXAMPLE 11

Preparation of 9-[4-nitroxy)butyroylamino]-1,2,3,4-tetrahydroacridine



(E-11)

The precursor drug is tacrine of formula



(E-11a)

The precursor compound of B is the 4-hydroxybutyric acid.

a) Preparation of 9-[4-bromo)butyroylamino]-1,2,3,4-tetrahydroacridine

To a solution of tacrine (4 g, 20.17 mmols) in chloroform (50 ml) and N,N-dimethylformamide (15 ml), 4-bromobutyroylchloride (3.5 ml, 30.25 mmols) is added. The reaction mixture is maintained under stirring at room temperature for 6 hours and then diluted with chloroform and washed with water. The organic phase, anhydrified with sodium sulphate, is evaporated at reduced pressure. The crude product is purged by chromatography on silica gel, eluting with n-hexane/ethyl acetate 8/2 (ratio by volume). 9-[4-bromo)butyroylamino]-1,2,3,4-tetrahydroacridine is obtained.

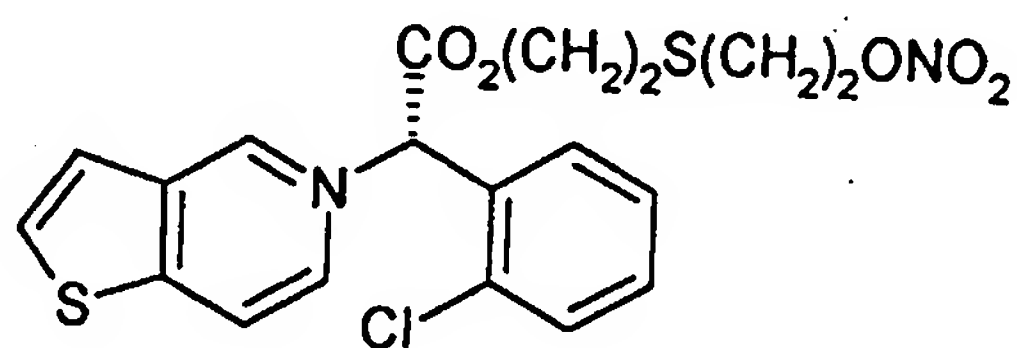
b) Preparation of 9-[4-nitroxy)butyroylamino]-1,2,3,4-tetrahydroacridine

To a solution of 9-[4-bromo)butyroylamino]-1,2,3,4-tetrahydroacridine (3.5 g, 10.56 mmoles) in acetonitrile (150 ml) silver nitrate (2.08 g, 12.68 mmoles) is added. The reaction mixture is heated at 80°C under stirring for 6 hours away from light. It is cooled to room temperature, filtered to remove the silver salts and evaporated under reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 8/2 (ratio by volume). 9-[4-nitroxy)butyroylamino]-1,2,3,4-tetrahydroacridine is obtained. Yield: 33%.

Elementary analysis:	C	H	N
Calculated	62.00%	5.81%	12.76%
Found	62.02%	5.83%	12.77%

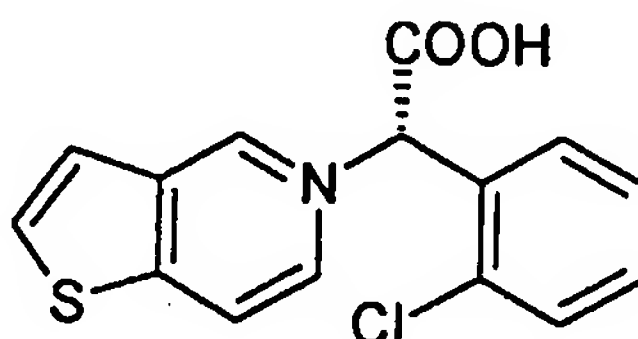
EXAMPLE 12

Preparation of (S)- α -(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]-pyridin-5(4H)acetic acid 5-(nitroxy)ethylthioethyl ester



(E-12)

The precursor drug is clopidrogel of formula:



(E-12a)

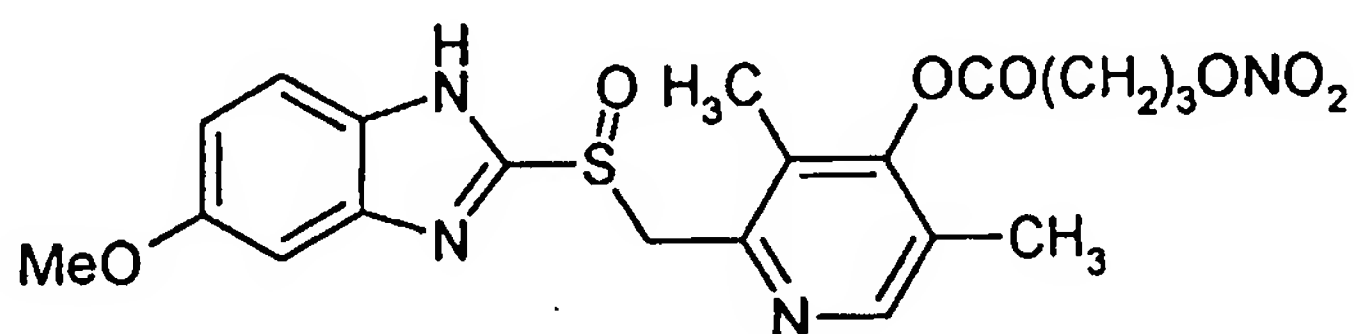
The precursor compound of A is the thiodiethylenglycol of formula $\text{HO}-(\text{CH}_2)_2-\text{S}-(\text{CH}_2)_2-\text{OH}$.

The compound of formula (E-12) is synthesized according to the procedure described in Example 5, using thiodiethylenglycol in substitution of diethylenglycol. Yield: 56%.

Elementary analysis:	C	H	N	Cl	S
Calculated	49.94%	4.63%	6.13%	7.76%	14.03%
Found	49.93%	4.63%	6.10%	7.75%	14.01%

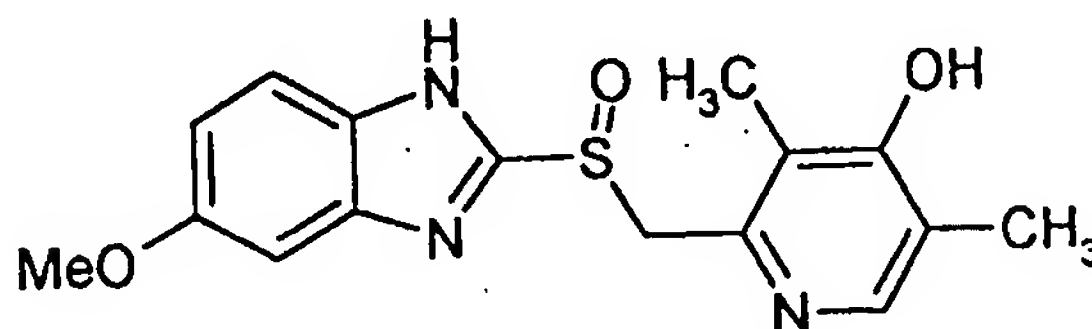
EXAMPLE 13

Preparation of 5-methoxy-2-[[4-(4-nitroxybutyryloxy)-3, 5-dimethyl-2-pyridinyl] methyl]sulphonyl]-1H-benzoimidazol



(E-13)

The precursor drug is demethylomeprazol of formula:



(E-13a)

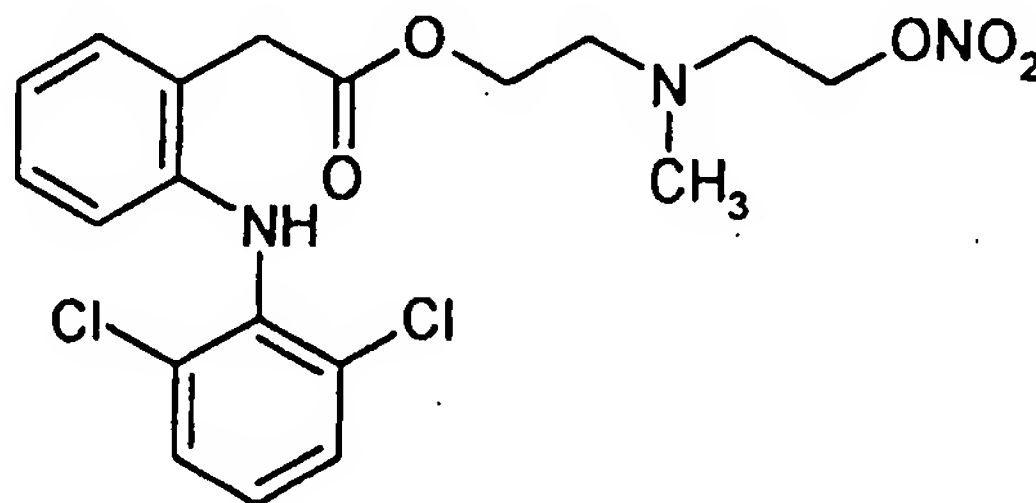
The precursor compound of B is 4-hydroxybutyric acid.

The compound of formula (E-13) is synthesized according to the procedure described in Example 1. Yield: 22%.

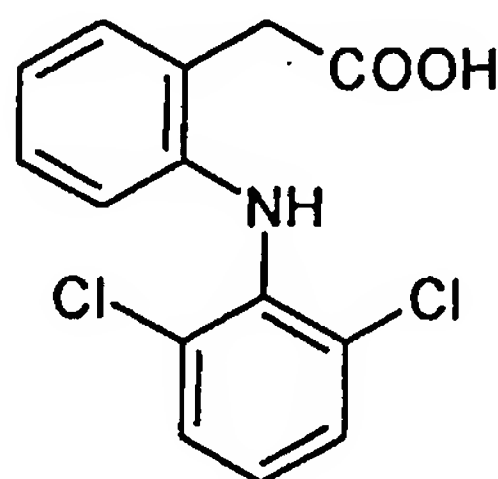
Elementary analysis:	C	H	N	S
Calculated	51.94%	4.79%	12.12%	6.93
Found	51.93%	4.77%	12.11%	6.94%

EXAMPLE 14

Preparation of 2-[(2,6-dichlorophenyl)amino]benzene acetic acid
[N-methyl-N-(2-hydroxyethyl)]-2-aminoethyl ester (E-14)



The precursor drug is diclofenac of formula:



(E-14a)

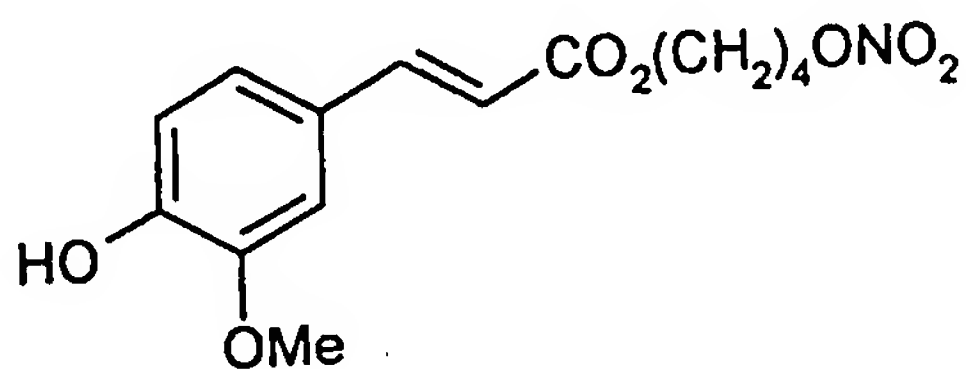
The precursor compound of B is N-methyldiethanolamine of formula $\text{HO}-(\text{CH}_2)_2-\text{N}(\text{CH}_3)-(\text{CH}_2)_2-\text{OH}$.

The compound is synthesized according to the procedure described in Example 5. Yield: 52%.

Elementary analysis:	C	H	N	Cl
Calculated	51.60%	4.78%	9.50%	16.03%
Found	51.60%	4.77%	9.53%	16.04%

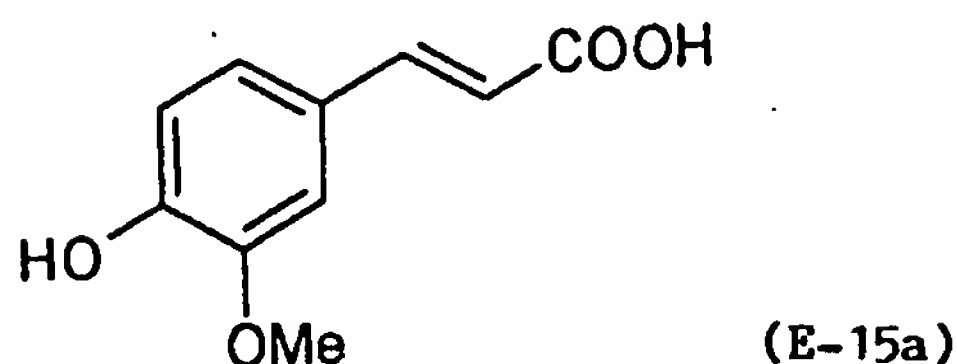
EXAMPLE 15

Preparation of 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid
4-(nitroxy)butylester



(E-15)

The precursor drug is ferulic acid of formula (E-15a)



The precursor compound of B is 1,4-butanediol.

a) Preparation of 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-bromo butyl ester

To a solution of ferulic acid (10 g, 51.51 mmol) in tetrahydrofuran (400 ml), triphenylphosphine (27 g, 103 mmol) and carbon tetrabromide (34.1 g, 103 mmol) are added. The reaction mixture is maintained under stirring at room temperature for 4 hours, then filtered and evaporated under reduced pressure. The reaction crude product is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 7/3 (ratio by volume). 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-bromo butyl ester is obtained.

b) Preparation of 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-(nitroxy)butyl ester

To a solution of 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-bromobutyl ester (2.72 g, 6.89 mmol) in acetonitrile (25 ml) silver nitrate (1.48 g, 8.71 mmol) is added. The reaction mixture is maintained under stirring and heated at 80°C for 7 hours away from light, then cooled at room temperature, filtered to remove the silver salts and evaporated under reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 7/3 (ratio by volume). 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-(nitroxy) butyl ester is obtained. Yield: 56%.

Elementary analysis:	C	H	N
Calculated	54.02%	5.50%	4.50%
Found	54.00%	5.52%	4.49%

PHARMACOLOGICAL TESTSEXAMPLE

Acute Toxicity

Acute toxicity has been evaluated by administering to a group of 10 rats weighing 20 g a single dose of each of the compounds to be tested, by cannula, by os in an aqueous 2% w/v suspension of carboxymethylcellulose.

The animals are kept under observation for 14 days. In no animal of the group toxic symptoms appeared even after a 100 mg/Kg dose administration.

EXAMPLE F1

Test 1 - experimental model in vivo with N-ethylmaleimide (NEM): study of the gastric tolerability of some drugs screened as precursors of the compounds of the invention.

The animals (rats, weight about 200 g) are distributed in the following groups (No. 10 animals for group):

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, physiologic solution when by parenteral route),

2° group: treatment: carrier + NEM,

B) Groups administered with each drug:

group I: treatment: carrier + drug,

group II: treatment: carrier + drug + NEM.

The drugs assayed in this experiment are the following (Table I): indomethacin, ambroxol, mesalamine, sodic alendronate, tacrine, omeprazol, misoprostol.

Indomethacin, ambroxol and alendronate are administered by os, mesalamine by intracolonic (rectal) route and tacrine, omeprazol, misoprostol by subcutaneous route.

The maximum tolerated dose, determined by administering each substance by the above said routes to the animals not treated with NEM, is reported in Table I. With higher doses than those reported in the Table, enteropathy, diarrhoea, depression, tremor and sedation have appeared in the animals.

In this experimental model the animals are at first treated with NEM by subcutaneous injection at a dose of 25 mg/kg in physiologic solution. The drug is administered one

hour later, in suspension in the carrier. Animals are sacrificed after 24 hours and evaluation of the damage to the gastrointestinal mucosa is made by counting the number of rats, inside each group, with lesions to the stomach at a visual inspection. The total number of said rats is then divided by the total number of rats of the group and multiplied by 100. The thus obtained percentages are reported in Table I. The Table shows that in the groups of rats treated with said drugs without NEM, no gastric lesions were detectable.

All the rats of group II (treated with NEM) showed gastric lesions after administration with the following drugs: indomethacin, ambroxol, mesalamine, sodic alendronate, tacrine. Said drugs therefore can be used in the synthesis of the products of the invention.

Omeprazol and misoprostol cannot instead be used, on the basis of the results provided in test 1, for preparing the products of the invention.

EXAMPLE F2

Test 2 (in vitro): inhibition of apoptosis (DNA fragmentation) induced in the endothelial cells by CIP in the presence of some drugs screened as precursors of the compounds of the invention.

The following precursor drugs (Table II): indomethacin, paracetamol, clopidogrel, salbutamol, ambroxol, sodic alendronate, diphylline, cetirizine, enalapril, nicotinamide, ampicilline, aciclovir, mesalamine, tacrine, simvastine, omeprazol have been tested.

Human endothelial cells of the umbilical vein are prepared according to a standard method. Fresh umbilical veins are filled with a collagenase solution 0.1% by weight and incubated at 37°C for 5 minutes.

Subsequently the veins are perfused with the medium M 199 (GIBCO, Grand Island, NY) pH 7.4 with 0.1% (weight/volume) of collagenase, added with 10% of bovine fetus serum (10 mcg/ml), sodium heparin (50 mcg/ml), thimidine (2.4 mcg/ml), glutamine (230 mcg/ml), penicillin (100 UI/ml), streptomycin (100 mcg/ml) and streptomycin B (0.125 mcg/ml). The cells are collected from the perfusate by centrifugation at 800 rpm and harvested in culture flasks T-75, pretreated with human fibronectin. Cells are then harvested in the same medium,

added with bovine hypothalamic growth factor (100 ng/ml). When the cells of the primary cell culture (the cells directly removed from ex-vivo umbilical vein) form a single layer of confluent cells (about 8,000,000 cells/flask), harvesting is stopped and the layers are washed and trypsinized. The cellular suspensions are transferred into wells of a culture plate having 24 wells, half of said wells being added with the same culture medium containing the drug at a 10^{-4} M concentration, and harvested in a thermostat at 37°C at a constant moisture (90%), $\text{CO}_2 = 5\%$. When the drug is not soluble in the culture medium, it is formerly dissolved in a small amount of dimethylsulphoxide. The maximum amount of dimethylsulphoxide which can be added to the culture medium is 0.5%. Only the cells coming from these first subcultures are used for the tests with cumene hydroperoxide (CIP). The cells are identified as endothelial cells by morphological examination and by the specific immunological reaction towards factor VIII; these cultures did never show contaminations from myocytes or fibroblasts.

Before starting the test, the cellular culture medium is removed and the cellular layers are carefully washed with a standard physiologic solution buffered with phosphate 0.1 M pH 7.0, at the temperature of 37°C. The content of each well is then incubated for one hour with a CIP suspension in the culture medium at a 5 mM concentration. Evaluation of the cellular damage (apoptosis) is carried out by determining the per cent variation of the DNA fragmentation in the cultures containing the drug + CIP with respect to the controls treated with CIP only. Said % variation of DNA fragmentation is determined by evaluating the fluorescence variation by a BX60 Olympus microscope (Olympus Co., Roma) set at the wave length of 405-450 nm, of the test samples with respect to the optical density of the controls. The fluorescence of each sample was determined on 5 replicates. Statistic evaluation has been made with t Student test ($p < 0.01$).

Results are given in Table II and show that indomethacin, paracetamol, clopidogrel, salbutamol, sodic alendronate, dipylline, cetirizine, enalapril, nicotinamide, ampicilline, aciclovir, tacrine, omeprazol do not significantly inhibit

apoptosis; these drugs can therefore be used for preparing the products of the invention.

On the contrary ambroxol, mesalamine and simvastatine inhibit apoptosis. Therefore on the basis of the results of test 2 these compounds could not be used for preparing the products of the invention.

EXAMPLE F3

Test 3 - experimental in vivo model with N^w-nitro-L-arginine-methyl ester (L-NAME): gastric tolerability (gastrointestinal damage incidence), hepatic (GPT dosage, glutamic-pyruvic transaminase) and cardiovascular (blood pressure) of some drugs screened as precursors of the compounds of the invention.

The experimental model adopted is according to J. Clin. Investigation 90, 278-281, 1992.

The endothelial dysfunction is evaluated by determining the damage induced by L-NAME administration to the gastrointestinal mucosa, the hepatic damage (GPT increase), and the vascular endothelium or cardiovascular damage as blood hypertension.

The animals (rats, average weight 200 g) are divided in groups as herein below described. The group receiving L-NAME is treated for 4 weeks with said compound dissolved at the concentration of 400 mg/litre in drinking water. The following groups (No. 10 animals for group) are constituted:

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, physiologic solution when by parenteral route),

2° group: treatment: carrier + L-NAME,

B) Groups treated with the drug:

3° group: treatment: carrier + drug,

4° group: treatment: carrier + drug + L-NAME.

The drugs used in the test are paracetamol, doxorubicine, simvastatine, omeprazol and misoprostol. Each drug is administered once a day for 4 weeks.

The maximum tolerated dose of the drug being administered to the animals is determined by evaluating, in a separate dose scaling up experiment on untreated animals, the appearance in

the animals of symptoms such as enteropathy, diarrhoea, depression, tremor, sedation.

At the end of the four weeks access to water is prevented and after 24 hours the animals are sacrificed.

One hour before the sacrifice blood pressure is determined and a blood pressure increase is taken as an indication of a damage being occurred to vascular endothelium.

The damage to the gastric mucosa is evaluated as previously mentioned in test 1 (ex. F1). The hepatic damage is determined by evaluation after the sacrifice of the glutamic-pyruvic transaminase (GPT increase).

The drug meets test 3 and it can therefore be used for preparing the compounds of the invention, when in the group of rats treated with L-NAME + drug + carrier, an higher hepatic damage (higher GPT values) and/or higher gastric damage and/or higher cardiovascular damage (higher blood pressure) are found in comparison with the group treated with the carrier only, or the group treated with carrier + drug, or the group treated with carrier + L-NAME.

The test results are reported in Table IV. The % gastric lesions have been determined as in Test 1. The % GPT and % blood pressure values are referred to the corresponding value found in the animals of the 1st group of the control groups. The average value of the blood pressure in this group was of 105 ± 8 mmHg.

The results obtained show that paracetamol, doxorubicine and simvastatine cause hepatic damage and gastroenteropathy (GPT values and the gastric lesions are % higher compared both with the corresponding groups treated with the drug, in the absence of L-NAME, and with the controls treated with L-NAME).

These drugs can therefore be used for preparing the products of the invention.

Omeprazol and misoprostol should not instead be used, on the basis of this test, for preparing the products of the invention.

EXAMPLE F4

Test 4A: Activity of some substances used as precursors of B in the products according to the invention in inhibiting the haemolysis of erythrocytes induced by cumene peroxide.

Test 4a is performed according to the method described by R. Maffei Facino, M. Carini G. Aldini, M.T. Calloni, Drugs Exptl. Clin. Res. XXIII (5/8) 157-165 1997.

Erythrocytes isolated by using standard procedures from Wistar male rats (Charles River), are suspended in a physiological solution buffered at pH 7.4 with phosphate buffer and equilibrated at 4°C for 4 days. then an aliquot of said suspension is centrifuged at 1000 rpm for 5 minutes and 0.1 ml of the centrifuged erythrocytes are diluted to 50 ml with sodium phosphate buffer of the same above molarity, thus obtaining a suspension containing 0.2% by volume of erythrocytes. 3.5 ml portions of said diluted suspension are added of 0.1 ml of an alcoholic solution of cumene hydroperoxide 9.72 mM, which causes lysis of the cells. The resulting suspension is then incubated at 37°C. An increase of the turbidity is observed in the suspension. The process of cell lysis is followed by turbidimetry at 710 nm, by determining the optical density (or the transmittance) at intervals of 30 minutes. The time at which there is the maximum amount of cell lysed, that corresponds to the maximum turbidity of the suspension, is taken as the T_{max} and it is assumed to correspond to a cell lysis of 100%. 0.2 ml of 38 mM ethanol solutions of the test compounds to be used as precursors of B are added to aliquots of 3.5 ml of the diluted suspension of erythrocytes above prepared, the resulting suspension preincubated for 30 minutes, 0.1 ml of an alcoholic solution of cumene hydroperoxide 10.26mM is then added, and at the time T_{max} it is determined the percentage of haemolysis inhibition in the sample from the ratio, multiplied by 100, between the absorbance of the suspension of the sample containing the erythrocytes, the precursor of B and cumene hydroperoxide respectively and that of the suspension containing the erythrocytes and cumene hydroperoxide; the precursors of B meet the test if they inhibit the haemolysis induced by cumene hydroperoxide by a percentage > 15%;

In Table V are reported the results obtained with the following substances: N-methyldiethanolamine, diethylenglycol, thio-diethylenglycol, 1,4-butandiol, butanol and diethanolamine.

Table V shows that:

- N-methyldiethanolamine, diethylenglycol, thiodiethylen glycol, 1,4-butandiol meet test 4 since they inhibit the haemolysis induced by cumene peroxide to an extent higher than 15%.
- Butanol and diethanolamine are instead ineffective, since they inhibit the haemolysis induced by cumene hydroperoxide to an extent lower than 15% and therefore they cannot be used as precursors of B in the synthesis of the compounds according to the present invention.

EXAMPLE F5

Test 5: Activity of compounds used as precursors of B in Inhibiting radical production from Fe^{II} compounds.

0.1 ml aliquots of 10^{-4} M methanolic solutions in methanol of, respectively, 1-4 butandiol, of N-methyl-diethanolamine of di-ethylenglycol and of thiodiethylenglycol, are added to test tubes containing an aqueous solution obtained by mixing 0.2 ml of 2 mM deoxyribose, 0.4 ml of buffer phosphate pH 7.4 100 mM and 0.1 ml of 1 mM $\text{Fe}^{\text{II}}(\text{NH}_4)_2(\text{SO}_4)_2$ in 2mM HCl. The test tubes are then kept at a temperature of 37°C for one hour. Then in each test tube are added in the order 0.5 ml of a 2.8% solution in trichloroacetic acid in water and 0.5 ml of an aqueous solution 0.1 M thio barbituric acid. A reference blank is constituted by substituting the above 0.1 ml aliquots of the test compound methanolic solutions with 0.1 ml of methanol. The test tubes are closed and heated in an oil bath at 100°C for 15 minutes. A pink coloration develops the intensity of which is proportional to the quantity of deoxyribose undergone to radical oxidative degradation. The solutions are cooled at room temperature and their absorbances at 532 nm are read against the blank.

The inhibition induced by the precursor of B in the confront of radical production from Fe^{II} is determined as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound + the iron salt and that of the solution containing only the iron salt.

The results are reported in the attached Table III, in

which it is shown that the compounds under test are ineffective in inhibiting the radical production from the iron ion.

Therefore these compounds can be used as precursor compounds of B for obtaining the compounds of the present invention.

EXAMPLE F6

It has been evaluated the activity of some of the compounds object of the present invention and of the corresponding precursor drugs in inhibiting DNA degradation (apoptosis) in endothelial cells exposed to the action of hydrogen peroxide (HP).

Hydrogen peroxide is a mild oxidant and is considered as an essential mediating agent in pathologies associated with oxidative stress (B. Halliwell, J. Gutteridge "Free Radicals in Biology and Medicine", page 416, 1993). Therefore the pharmacological activity of compounds to be used under oxidative stress conditions is evaluated through their capability of neutralizing the cytolesive effects of the hydrogen peroxide (B. Halliwell, J. Gutteridge "Free Radicals in Biology and Medicine", page 416, 1993).

The method described by Herman et Al. (Herman C., Zeiner M.A., Dimmeler S., Arterioscler. Thromb. Vasc. Biol. 17 (12), 3588-82, 1997).

Human endothelial cells of the umbilical vein are prepared according to a standard method. Fresh umbilical veins, just removed, are filled with a solution of collagenase at 0.1% and incubated at 37°C for 5 minutes.

Subsequently the veins are perfused with medium M 199 (GIBCO, Grand Island, NY) pH 7.4 containing 20% of human serum. The cells are collected from the perfusate by centrifugation at 800 rpm and harvested in culture flasks T-75, pretreated with human fibronectin. Cells are then harvested in the medium pH 7.4, containing 20% human serum, low molecular weight sodium heparin (30 mcg/ml), penicillin (100,000 UI/ml) and bovine hypothalamic growth factor (100 ng/ml). The primary confluent monolayers (about 8,000,000 cells/flask) are washed and trypsinized. The cellular suspensions are transferred into each well of a culture plate with 24 hollows and harvested in a thermostat at 37°C at constant humidity (90%), CO₂ = 5%. Only

the cells coming from these first subcultures are used for the experiments with HP. The cells are identified as endothelial cells by morphological examination and by specific dye-reactions. The cultures never showed contaminations from myocytes or fibroblasts.

In order to perform the experiment with HP, the cellular culture medium is removed and the cellular layers are carefully washed with a physiological solution buffered with 0.1 M phosphate pH 7.0 at the temperature of 37°C. The cells are then incubated for 18 hours with HP at the concentration of 200 μ moles/l.

The evaluation of the cellular damage (apoptosis) is carried out by determining the percent variation of the DNA fragmentation in the sample with respect to the control added only of HP. The products under assay are tested at the concentration of 100 μ moles/l. If said products are found insoluble in the culture medium, they are dissolved in a small amount of dimethylsulphoxide (DMSO), taking into account that the maximum DMSO amount which can be added to the culture medium is 0.5% v/v. 3 replicates of each sample are made.

The results are reported in Table VI and show that in those samples of cell culture treated with the compounds of the invention, the inhibition of the DNA fragmentation, or in more general terms of cellular damage, is at least twice than that occurring in the samples treated with the corresponding precursors.

EXAMPLE F7

Gastric lesions induced by administration of the compounds of the invention in the confront of the corresponding drug precursor.

Groups of male Wistar rats weighing 180-200 g (No. 10 rats for group), fasted from 17 hours, have been fed by os, by a cannula, with a 2% carboxymethylcellulose suspension in water (carrier) added with one of the following compounds:

- Diclofenac, dose of 20 mg/kg p.o.,
- Diclofenac nitroxyester according to Ex. 14, at the same above dose p.o.,
- Ambroxol, 100 mg/kg p.o.,
- Ambroxol nitroxyester according to Example 3 at the same

- above dose p.o.,
- Alendronate, dose 100 mg/kg p.o.,
 - Nitroxyester of the alendronic acid according to Ex. 4 at the same above dose, p.o.

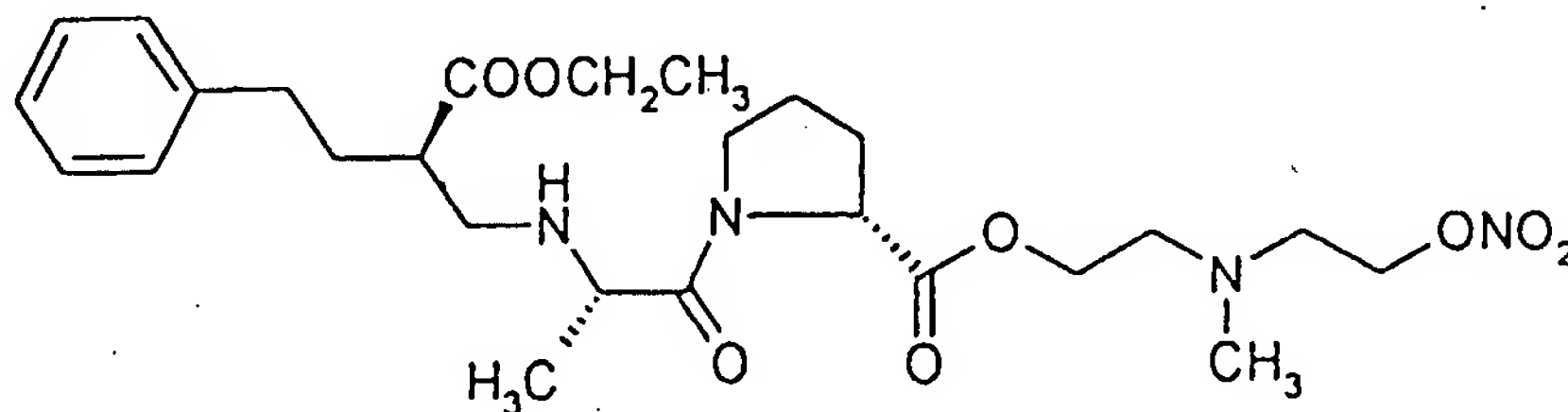
Tacrine and the corresponding nitroxyester obtained according to Ex. 11, have been administered to the rats by subcutaneous route in a physiological solution at the dose of 10 mg/kg.

The animals have been sacrificed 6 hours after the administration. The gastrointestinal mucosa has been removed and inspected. The incidence of the gastrointestinal damage has been evaluated as described in experiment F1.

The results are reported in Table VII and show that the compounds of the invention do not either induce gastric lesions or, in the case, the incidence of said lesions is much lower than that found with the precursor drug.

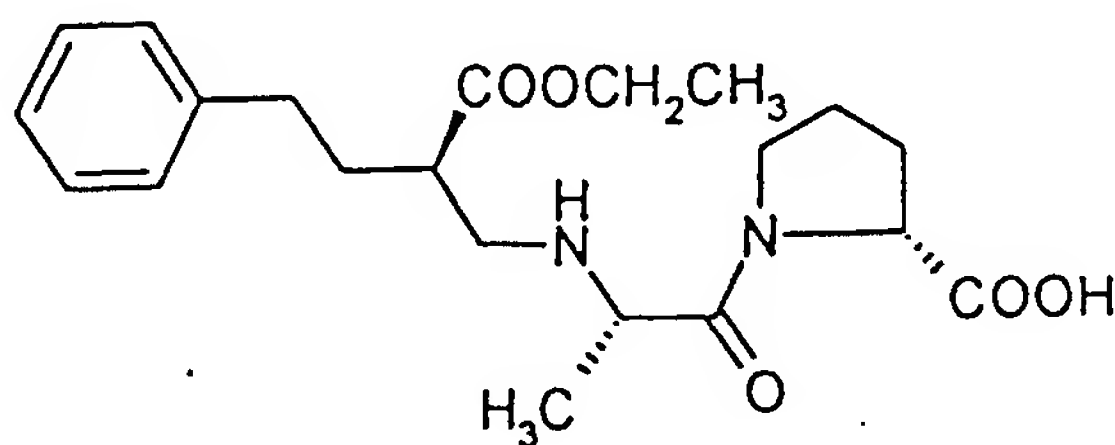
EXAMPLE 16

Synthesis of (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline[2-(N-methyl,N'-(2-nitroxy)ethyl)-ammino] ethyl ester of formula



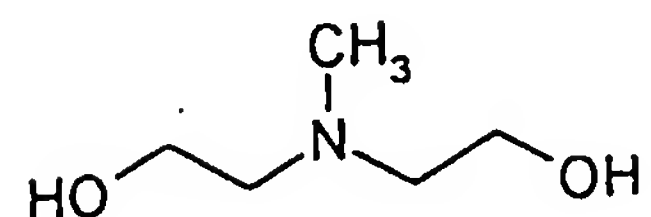
(E-16).

The precursor is enalapril having formula:



(E-16a)

and the precursor of B is N-metil-diethanolamine of formula:



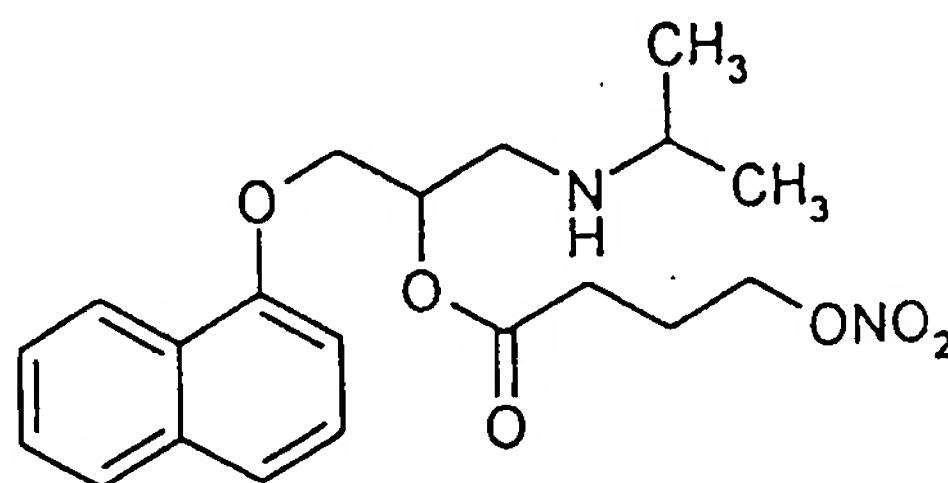
The compound of formula (E-16) is synthetized according to the process described in Example 5. Yield: 19%

Elemental analysis:

Calculated %	C 58,19	H 7,51	N 10,44
Found %	C 58,22	H 7,53	N 10,42

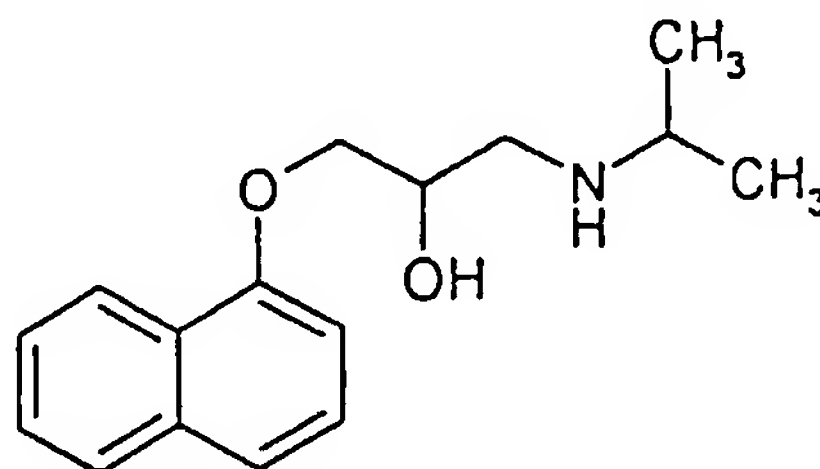
EXAMPLE 17

Synthesis of (4-nitroxy)-butanoic acid 1-[(1-methylethyl) amino]-3-(1-naphthalen oxy)-2-propyl ester of formula



(E-17)

The precursor is propranolol having the following formula:



(E-17a)

and the precursor of B is 4-hydroxy-butanoic acid.

Compound (E-17) is synthetized according to Example 1.

Yield: 25%.

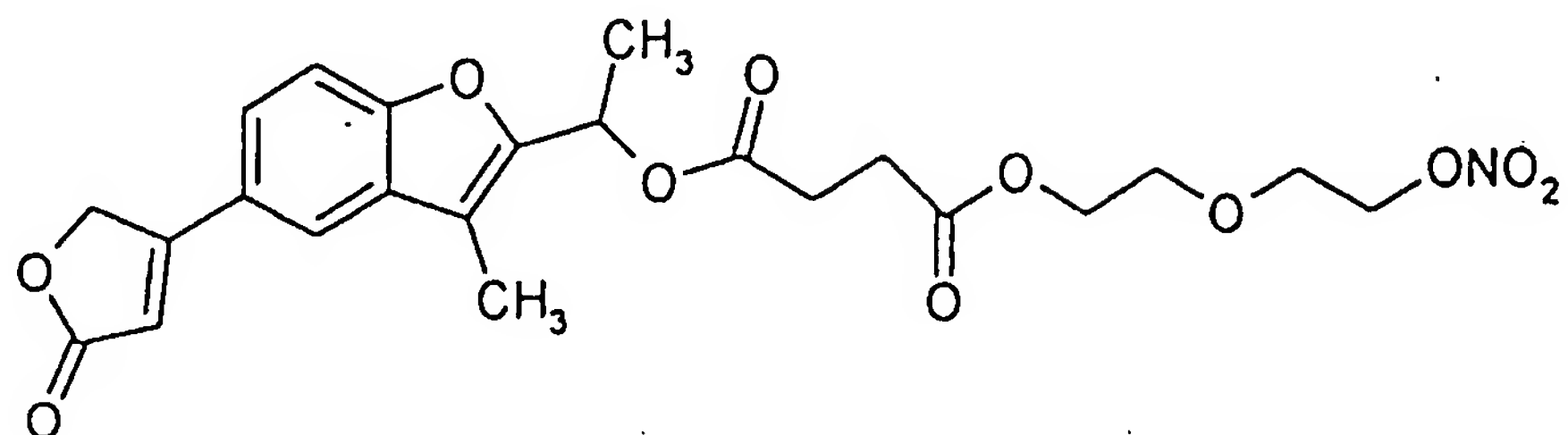
Elemental analysis:

Calculated %	C 61,53	H 6,71	N 7,17
Found %	C 61,58	H 6,74	N 7,15

EXAMPLE 18

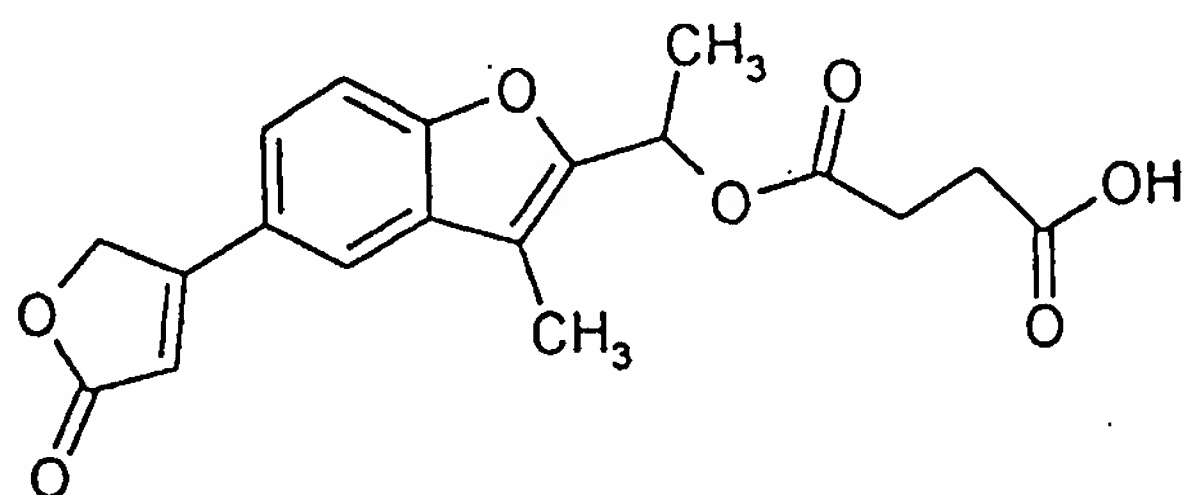
Synthesis of butandioic acid [1-[5-(2,5-dihydro-5-oxo-3-

furanyl)-3-methyl-2-benzofuranyl]ethyl [(2-nitroxy)ethoxy]
ethyl diester of formula



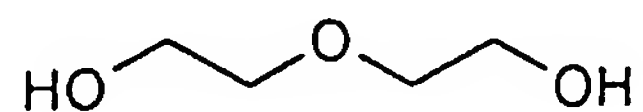
(E-18)

The precursor drug is Benfurodil hemisuccinate having
formula:



(E-18a)

and the compound precursor of B is diethylene glycol of
formula:



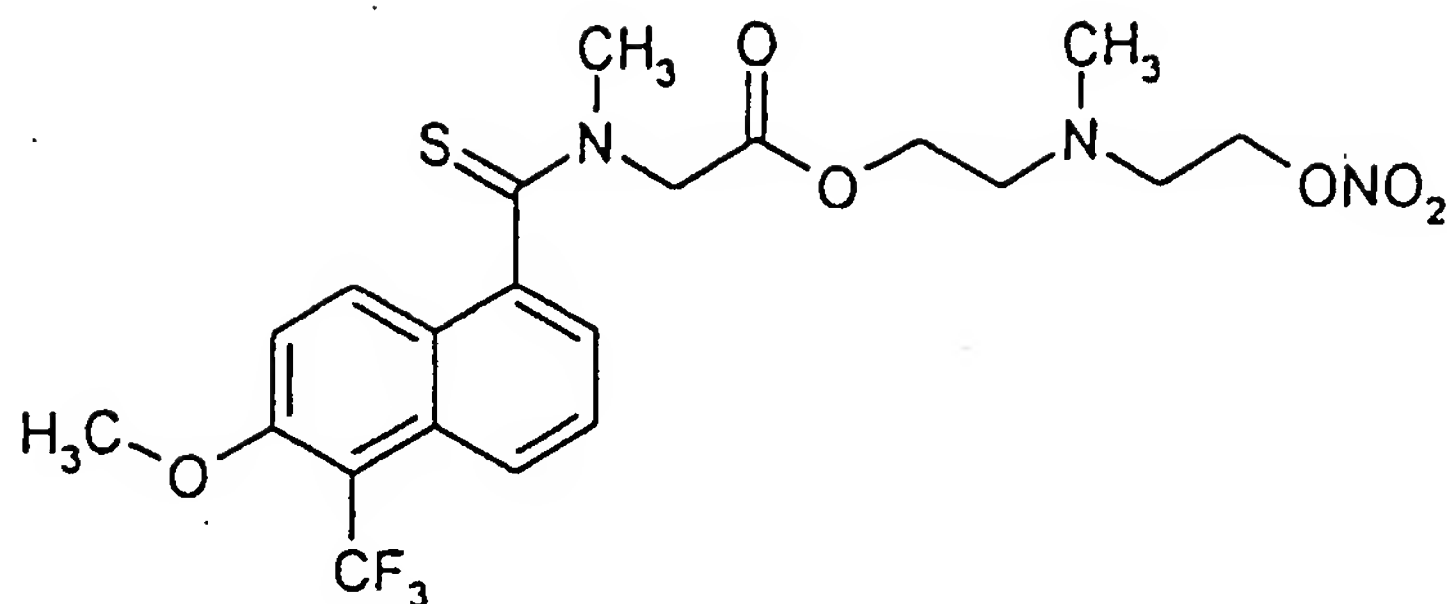
Compound (E-18) is synthesized according to Example 6.
Yield: 16%.

Elemental analysis:

Calculated %	C 56,21	H 5,13	N 2,85
Found %	C 56,26	H 5,10	N 2,90

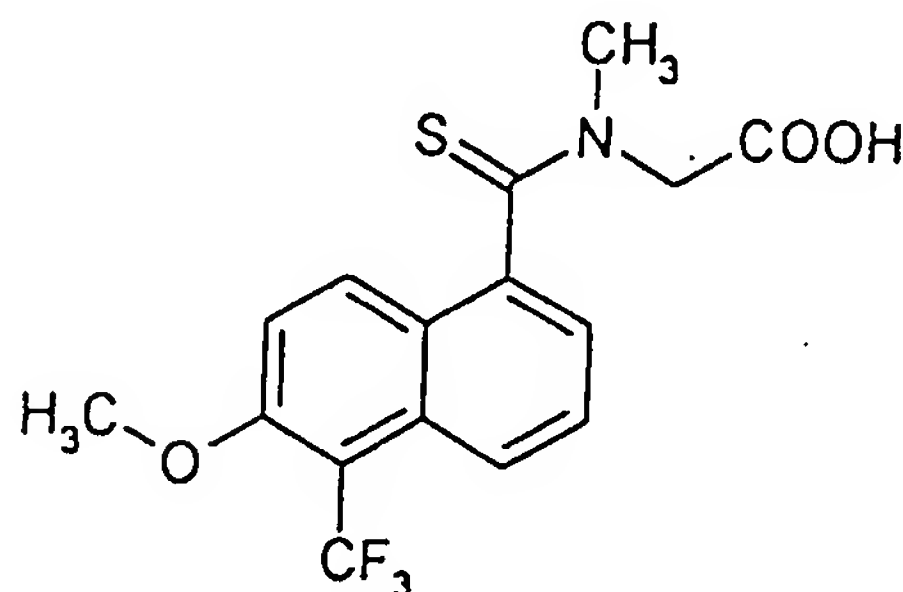
EXAMPLE 19

N-[[6-methoxy-5-(trifluoromethyl)-1-naphtalenyl[thioxomethyl]
-N-methylglycine [2-(N-methyl,N'-(2-nitroxy)ethyl)ammino]
ethyl ester of formula



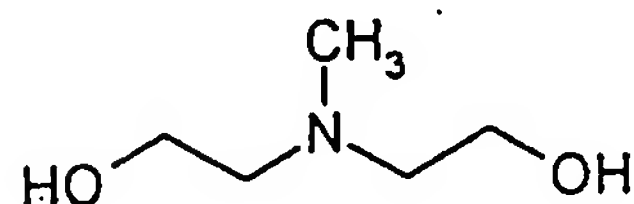
(E-19)

The precursor drug is tolrestat of formula:



(E-19a)

and the precursor of B is N-metil diethanolamine of formula:



Compound (E-19) was synthetized according to Example 5.

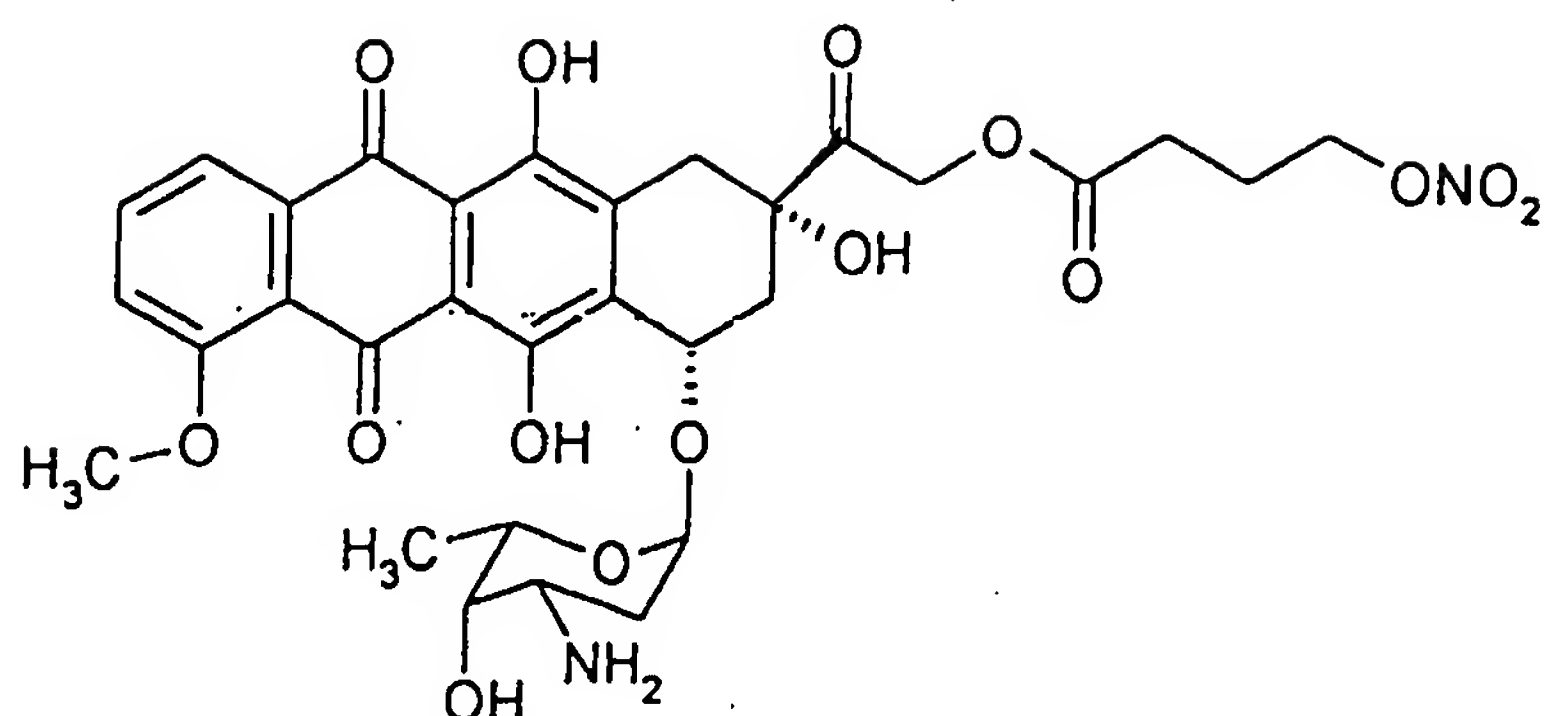
Yield: 12%

Elemental analysis:

Calc. %	C 50,10	H 4,80	N: 8,35	S 6,30	F 11,32
Found %	C 50,15	H 4,82	N 8,30	S 6,25	F 11,34

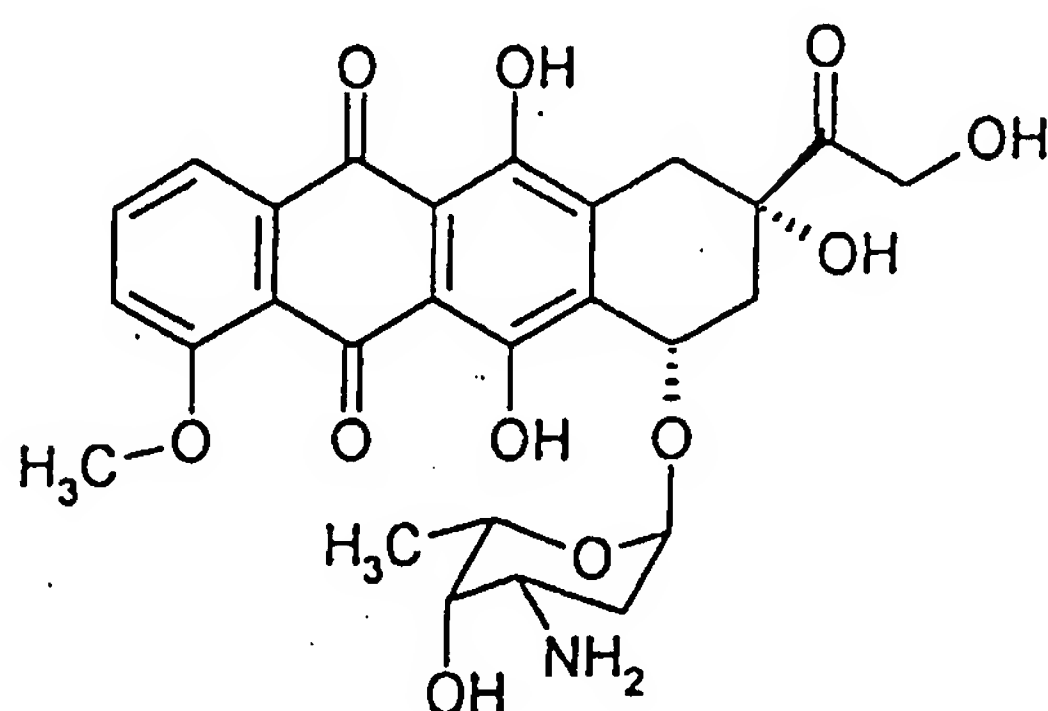
EXAMPLE 20

Synthesis of (8S-cis)-10[(3-amino,2,3,6-tri-deoxy- α -L-lyxo-exopyranosyl)oxy]-7,8,9,10-tetrahydro,6,8,11-trihydroxy-8-[[3-methoxy-4-(4-nitroxy butanoyl-oxy) methyl-oxo]-1-methoxy-5,12-naphtacenedione of formula



(E-20)

The precursor drug is doxorubicin of formula:



(E-20a)

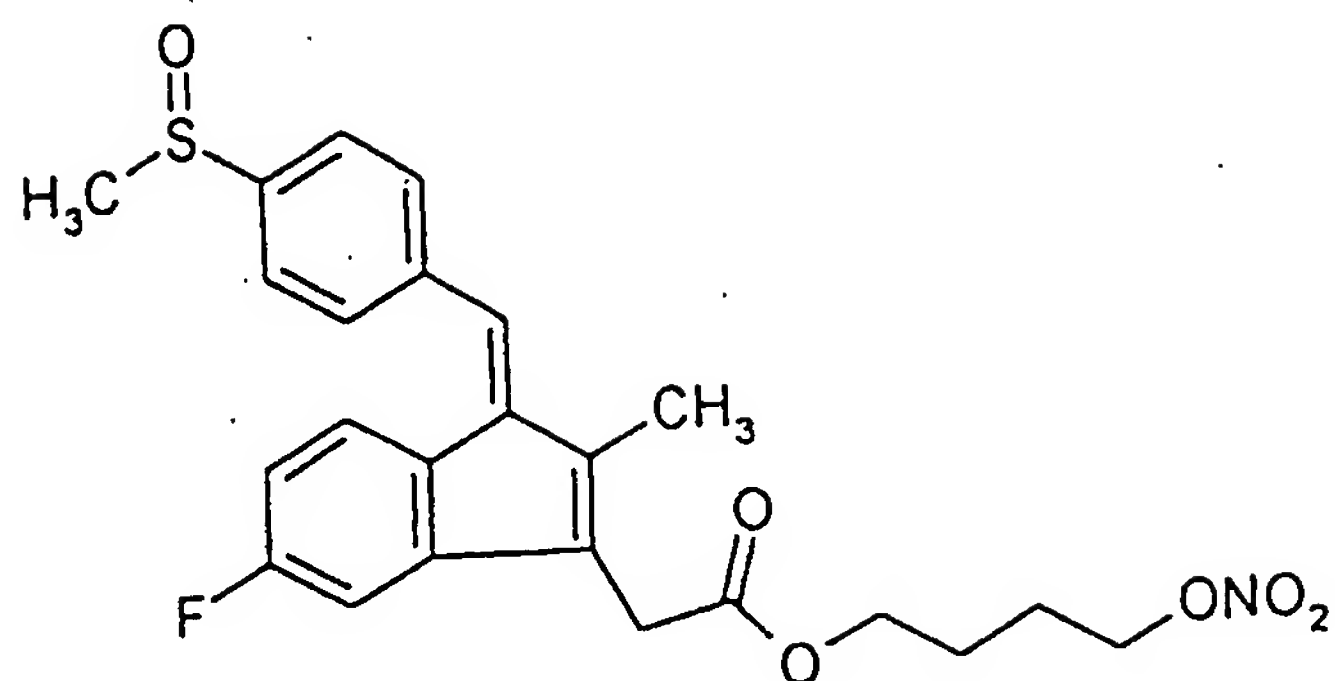
The compound precursor of B is 4-hydroxy-butyric acid
Compound (E-20) is synthesized according to the process of
Example 1. Yield: 12%

Elemental analysis:

Calculated %	C 55,19	H 5,08	N 28,01
Found %	C 55,21	H 5,09	N 28,08

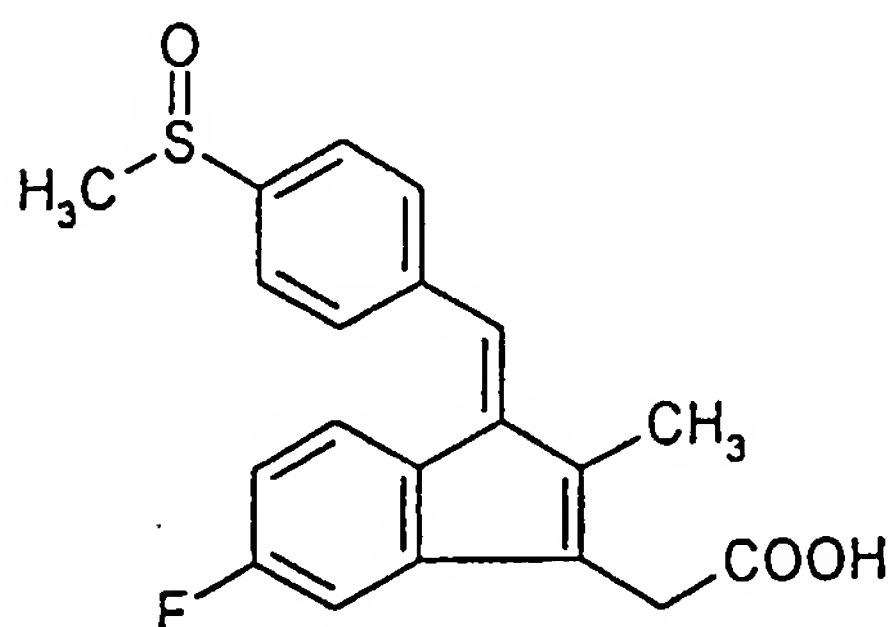
EXAMPLE 21

Synthesis of (Z)-5-fluoro-2-methyl-1-[[4-(methyl sulphanyl)phenyl]methylene]-1H-indene-3-acetic acid (4-nitroxy)butyl ester of formula:



(E-21)

The precursor drug is Sulindac of formula:



(E-21a)

and the precursor of B is 1,4-butandiol

a) Preparation of cis-5-fluoro-2-methyl-1-[p-(methylsulfinyl)benzyliden]indene-3-acetic acid 4-bromo butyl ester

To a solution of sulindac (5.17 g, 14.5 mmole) in dimethylformamide (50 ml) EtONa (1.18 g, 16.4 mmole) is added. The reaction mixture is kept under stirring for one hour, then a solution of 1,4-dibromobutane in dimethylformamide (20 ml) is added.

The reaction mixture is stirred at room temperature for 8 hours, then diluted with ethyl ether and washed with water. The organic phase is dehydrated on sodium sulphate and then evaporated at a reduced pressure. The raw product thus obtained is purified by column chromatography on silica gel, the eluent being n-hexane /ethyl acetate 3/7 (ratio by volume). It is obtained cis-5-fluoro-2-methyl-1-[p-(methylsulfinyl)]

benzyliden]indene-3-acetic acid 4-bromobutyl ester.

b) Preparation of cis-5-fluoro-2-methyl-1-[p-(methylsulphiny)]benzyliden]indene-3-acetic acid 4-(nitroxy)butyl ester

To a solution of cis-5-fluoro-2-methyl-1-[p-(methylsulfinyl)benzyliden]indene-3-acetic acid 4-bromobutyl ester (5.01 g, 10.18 mmole) in acetonitrile (60 ml) silver nitrate is added (3.5 g, 20.6 mmole). The reaction mixture is stirred at a temperature of 80°C for 48 hours in the absence of light, then cooled at room temperature and filtered to remove the formed insoluble silver salts and evaporated under a reduced pressure. The residue is purified by column chromatography on silica gel, eluted with n-hexane/ ethyl acetate 3/7 (ratio by volume). After evaporation of the solvent it is obtained (Z)-5-fluoro-2-methyl-1-[[4-(methyl sulphiny)]phenyl]methylene]-1H-indene-3-acetic acid (4-nitroxy)butyl ester (m.p. 93-97). Yield 40%.

Elemental analysis:

Calc. %	C	60.87	H	5,11	F	4,01	N	2,96	S	6,77
Found %	C	60.85	H	5,13	F	3,93	N	2,94	S	6,75

EXAMPLE F8

Example F1 was repeated with three groups of rats (each group of of ten animals), all of them receiving NEM, and orally administered as it follows :

- control group : the vehicle formed of an aqueous suspension 1% w/v of carboxymethylcellulose,
- one group (group b - comparative) administered at the same time with 10 mg/Kg (0.034 mmoles/Kg) of diclofenac + 4 mg/Kg (0.034 mmoles/Kg) of N-methyldiethanolamine in the same above vehicle,
- one group (group c) administered with 15 mg/Kg (0.034 mmoles/Kg) of the ester derivative of diclofenac according to the invention (ref. ex. 14), in the above same vehicle.

The results are reported in Table VIII and show that the mixture administered to group b (comparative), was much less effective in reducing gastric lesions than the group (group c) treated with the derivative according to the invention.

EXAMPLE F9

Antiinflammatory and analgesic activity of 4-(nitrooxy)butanoic acid 4-(N-acetylamino)phenyl ester (NO-paracetamol)

and of the precursor paracetamol.

Foreword

The principal therapeutic effects of NSAIDs derives from their ability to inhibit prostaglandin production ("Goodman & Gilman's, The Pharmacological Basis of Therapeutics" 9th Ed. 1996, McGraw Hill page 620) and the agents are classified on the basis of said principle. Sulindac and paracetamol have different mechanism from most currently used NSAIDS in view of their negligible ability to inhibit prostaglandin production. Both they interact with oxygen free radicals.

Antiinflammatory and analgesic activity have been measured according to carrageenan rat paw edema and acetic acid mouse writhing methods. Rats (male, wistar 100-150 g. and mice (male, LACA, 22-35 g) were used. NO-paracetamol, paracetamol or vehicle were given as carboxymethylcellulose suspension (0.5% w/v) in a volume of 1 mg/Kg.

Carrageenan paw edema

Experiments were conducted as described by Al-Swayeh et al., Brit. J. Pharmacol. 129, 343-350 2000). Hind paw volume was determined by plethysmography before and after 3 h after interplantar carrageenan injection (100 microliter, 2% w/v). The compounds were given intraperitoneally 15 ml prior to carrageenan injection. At the end of the experiment animals were killed by cervical dislocation and exsanguination. The Results shown in Table IX are expressed as % of paw edema inhibition, i.e. the paw volume of the controls (vehicle) subtracted of the paw volume of the treated and the obtained difference divided by the paw volume of the controls.

Acetic acid writhing

Experiments were conducted as described by Moore et al. (Br. J. Pharmacol. 102, 198-202 1990). The compounds were given orally 15 minutes prior to intraperitoneal acetic acid (2% w/v in saline pH 2.7, 10ml/Kg). Mice were transferred immediately to individual observation cages and the number of abdominal constrictions monitored over the following 30 minutes. At the end of the observation period the animals were killed by cervical dislocation and exsanguination. Results are expressed as the number of abdominal costrictions (writhings) per 30 minutes test period, expressed as percentage to those observed

in the control group, and are reported in Table IX.

The results of the Table demonstrate that NO-paracetamol is much more active in both tests than paracetamol.

EXAMPLE F10

Liver safety following administration of NO-paracetamol and paracetamol

Rats received either NO-paracetamol (1.4 g/Kg i.p.) or paracetamol (1.16 g/Kg i.p.) or vehicle (0.9% w/v NaCl containing 20% v/v tween-20). After 6 hours the animals were killed by cervical dislocation, trunk blood collected and plasma analysed for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity, liver glutathione and bilirubin concentration.

Glutathione depletion induced by paracetamol is considered a sign of oxidative stress (B. Halliwell, J. Gutterbridge "Free radicals in biology and medicine" 1993, Clarendon Press, pages 334-335).

The results are reported in Table X and are expressed as the percentage calculated on the corresponding values of the vehicle group (100%).

The results demonstrate that administration of paracetamol causes hepatic damage, as from the values of transaminases AST and ALT, and of bilirubin in respect of those of the controls.

Administration of NO-paracetamol induces much lower increases of AST and ALT, whereas the bilirubin concentration is lower than that in the control groups.

Thus, unlike paracetamol, NO-paracetamol is able to spare the liver, even in conditions of oxidative stress (i.e. hepatic glutathione is similarly depleted with paracetamol and NO-paracetamol).

Table I

Test 1 : Gastric tolerability of drugs representative of the drug classes illustrated in the present invention in animals not treated or treated with NEM (oxidative stress conditions). The % incidence is calculated from the ratio between the number of animals found with gastric lesions and that total of the group.			
Compound	dose (mg/Kg) /admin. route	Gastro-enteropathy (% incidence)	
		without NEM	with NEM
carrier		0	0
Indomethacin	7.5/p.o.	0	100
Ambroxol	25/p.o.	0	80
Mesalamine	750/i.c.	0	60
Alendronate	15/p.o.	0	90
Tacrine	1/s.c.	0	100
Omeprazol	30/s.c.	0	0
Misoprostol	0.5/s.c.	0	0

p.o. = per os; i.c. = by intracolonic route;
s.c. = by subcutaneous route.

Table II

Test 2 : Inhibition of apoptosis (DNA fragmentation) induced by CIP in the endothelial cells in the presence of compounds representative of the drug classes illustrated in the present invention.	
Compound	Apoptosis % with respect to the controls treated only with CIP
Indomethacin	95
Paracetamol	120
Clopidogrel	110
Salbutamol	90
Ambroxol	70
Alendronate	160
Diphylline	95
Cetirizine	115
Enalapril	80
Nicotinamide	98
Doxorubicin	94
Acyclovir	95
Mesalamine	74
Tacrine	90
Simvastatin	72
Omeprazol	90

Table III

Test 5 : Screening of the effectiveness of the listed substances to inhibit radical production induced by Fe ^{II}	
Compound	% Radical inhibition from Fe ^{II}
blank	0
N-methyldiethanolamine	0
Diethylenglycol	0
1,4-Butandiol	0
Thiodiethyleneglycol	0

Table IV

Test 3 : Gastric tolerability (gastrointestinal damage incidence), hepatic (GPT dosage, glutamic-pyruvic transaminase), and cardiovascular (blood pressure) of some compounds representative of the drug classes illustrated in the present invention under conditions of endothelial trouble induced by L-NAME. The results relating to the blood pressure and GPT are expressed as % values compared with those found in animals treated with the only carrier, without L-NAME.							
Compound	dose mg/Kg /administ. route	Blood pressure %		GPT %		Gastroenteropathy %	
		without L-NAME	with L-NAME	without L-NAME	with L-NAME	without L-NAME	with L-NAME
Carrier		100	152	100	155	0	30
Paracetamol	300/i.p.	108	155	180	500	20	90
Doxorubicin	1/i.p.	120	145	195	360	30	100
Simvastatin	50/p.o.	85	148	122	220	0	60
Omeprazol	30/s.c.	100	150	100	160	0	10
Misoprostol	0.5/s.c.	100	142	100	160	0	5

Table V

Test 4A: Screening of the effectiveness of the listed substances to inhibit erythrocyte haemolysis induced by cumene hydroperoxide	
Compound	% Haemolysis inhibition
N-Methyldiethanolamine	54.4
Diethylenglycol	33.4
Thiodiethylenglycol	26
1,4-Butandiol	17.4
Butanol	10.5
Diethanolamine	2.5

Table VI

Experiment F6: Apoptosis inhibition (DNA fragmentation) induced in endothelial cells by hydrogen peroxide, by precursors representative of the drug classes described in the present invention and of the corresponding derivatives of the invention.	
Compound	Apoptosis % (respect to the controls treated only with CIP)
Carrier	0
Diclofenac (comp.)	15
Diclofenac nitroxyester Es. 14	72
Ambroxol (comp.)	25
Ambroxol nitroxyester Ex. 3	50
Alendronate (comp.)	18
Alendronate nitroxyester Ex. 4	54
Tacrine (comp.)	8
Tacrine nitroxyester Ex. 11	73

Table VII

Experiment F7: screening of the gastric tolerability of the derivatives according to the present invention compared with that of the precursor drugs		
Treatment	dose mg/kg	Gastropathy % incidence
Carrier	-	0
Diclofenac (comp.)	20 p.o.	70
Diclofenac nitroxyester Es. 14	20 p.o.	0
Ambroxol (comp.)	100 p.o.	60
Ambroxol nitroxyester Ex. 3	100 p.o.	10
Alendronate (comp.)	100 p.o.	100
Alendronate nitroxyester Ex. 4	100 p.o.	10
Tacrine (comp.)	10 p.o.	60
Tacrine nitroxyester Ex. 11	10 s.c.	20

Table VIII

Test on gastric tolerability following oral administration of NEM (Ex. F8)		
groups	dose mg/Kg p.o.	Gastropathy % incidence
controls	-	-
group b - comparative mixture diclofenac (A) + N-methyldiethanolamine (B)	10(A) + 4(B)	50
group c diclofenac derivative according to the invention (ref. ex. 14)	14	20

Table IX

Antiinflammatory and analgesic activity of NO-paracetamol and paracetamol.		
Treatment	Antiinflammatory activity % paw edema inhibition	Analgesic activity % writhing inhibition
vehicle	-	-
paracetamol	34	40
NO-paracetamol	69	490

Table X

Liver safety assayed by AST (aspartate aminotransferase) ALT (alanine aminotransferase), glutathione and bilirubin concentration in animals treated with NO-paracetamol and paracetamol. The values given in the Table are expressed as % to the corresponding of the control group.				
Treatment	AST %	ALT %	Glutathione %	Bilirubin %
vehicle	100	100	100	100
paracetamol	330	171	52	200
NO-paracetamol	160	57	49	136

CLAIMS

1. Compounds or their salts having the following general formula (I):



wherein:

s is an integer equal to 1 or 2, preferably s = 2;

A = R—T₁·, wherein

R is the drug radical and

T₁ = (CO)_t or (X)_{t'}, wherein X = O, S, NR_{1c}, R_{1c} is H or a linear or branched alkyl, having from 1 to 6 carbon atoms, or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = -T_B—X₂—O· wherein

T_B = (CO) when t = 0, T_B = X when t' = 0, X being as above defined;

X₂, bivalent radical, is such that the corresponding precursor of B does not meet test 5 and meets test 4A; said precursor having formula -T_B—X₂·OH, wherein T_B = (CO) and t = 0, the free valence of T_B is saturated with:

-OZ wherein Z = H or R_{1a}, R_{1a} being linear or branched when possible C₁-C₁₀ alkyl, preferably C₁-C₅, or with -Z^I-N-Z^{II}, Z^I and Z^{II} being equal or different from each other, having the Z values, when T_B = X and t' = 0, the free valence of T_B is saturated with H;

with the proviso that:

the drug A = R—T₁·, wherein the free valence is saturated as hereinafter mentioned:

- when t' = 0 with:

- O-Z wherein Z = H or R_{1a} as above defined, or with

- Z^I-N-Z^{II},
|

Z^I and Z^{II} being as above defined,

- when t = 0 with X-Z, wherein X and Z as above defined,

is such as to meet at least one of tests 1-3;

- wherein test 1 (NEM) is a test in vivo carried out on

four groups of rats (each formed by 10 rats), the controls (two groups) and the treated (two groups) of which one group of the controls and one group of the treated respectively are administered with one dose of 25 mg/kg s.c. of N-ethylmaleimide (NEM), the controls being treated with the carrier and the treated groups with the carrier + the drug of formula $A = R-T_1$ wherein the free valence is saturated as above indicated, administering the drug at a dose equivalent to the maximum one tolerated by the rats that did not receive NEM, i.e. the highest dose administrable to the animal at which there is no manifest toxicity, i.e. such as to be symptomatologically observable; the drug complies with test 1, i.e. the drug can be used to prepare the compounds of general formula (I), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in the group treated with NEM + carrier + drug are observed gastrointestinal damages greater than those of the group treated with the carrier, or of the group treated with the carrier + drug, or of the group treated with the carrier + NEM;

- wherein test 2 (CIP) is a test in vitro wherein human endothelial cells from the umbilical vein are harvested under standard conditions, then divided into two groups (each group replicated five times), of which one is treated with a mixture of the drug 10^{-4} M concentration in the culture medium, the other group with the carrier; then cumene hydroperoxide (CIP) having a 5 mM concentration in the culture medium is added to each of the two groups; the drug meets test 2, i.e. the drug can be used to prepare the compounds of general formula (I), when a statistically significant inhibition of the apoptosis (cellular damage) induced by CIP is not obtained with $p < 0.01$ with respect to the group treated with the carrier and CIP;

- wherein test 3 (L-NAME) is a test in vivo carried out on four groups of rats (each group formed by 10 rats) for 4 weeks and receiving drinking water, the controls (two groups) and the treated (two groups), of which one group of the controls and of the treated respectively receives

in the above 4 weeks drinking water added of N- ω -nitro-L-arginine methyl ester (L-NAME) at a concentration of 400 mg/litre, the controls in the 4 weeks being administered with the carrier and the treated in the 4 weeks with the carrier + the drug, administering the carrier or the drug + carrier once a day, the drug being administered at the maximum dose tolerated by the group of rats not pretreated with L-NAME, i.e., the highest dose administrable to animals at which no manifest toxicity appears, i.e. such as to be symptomatologically observable; after the said 4 weeks, the water supply is stopped for 24 hours and then sacrificed, determining the blood pressure 1 hour before sacrifice, and after sacrifice of the rats determining the plasma glutamic pyruvic transaminase (GPT) after sacrifice, and examining the gastric tissue; the drug meets test 3, i.e. the drug can be used to prepare the compounds of general formula (I), when in the group of rats treated with L-NAME + carrier + drug, greater hepatic damages (determined as higher values of GPT) and/or gastric and/or cardiovascular damages (determined as higher values of blood-pressure) are found in comparison respectively with the group treated with the carrier alone, or with the group treated with the carrier + drug, or with the group treated with the carrier + L-NAME;

wherein test 4A which must be met by the compound precursor of B is a test in vitro wherein a portion of an erythrocyte suspension formerly kept at 4°C for 4 days, said erythrocyte isolated by standard procedures from Wistar male rats and suspended in a physiological solution buffered at pH 7.4 with phosphate buffer, is centrifuged at 1000 rpm for 5 minutes and 0.1 ml of the centrifuged erythrocytes are diluted with sodium phosphate buffer pH 7.4 at 50 ml; aliquots of 3,5 ml each (No. 5 samples) are taken from said diluted suspension and incubated at 37°C in the presence of cumene hydroperoxide at a concentration 270 μ M and the suspension turbidity determined at 710 nm at intervals of 30 minutes to establish the time (T_{max}) at which occurs the maximum turbidity, that corresponds to the maximum amounts of cells lysed by cumene hydroperoxide

(haemolysis assumed to be = 100%); then alcoholic solutions of the compounds precursors of B are added to 3.5 ml aliquots of the diluted suspension of centrifuged erythrocytes (tests carried out on 5 samples for each precursor of B assayed) in order to have a final concentration 2 mM of the precursor of B and then the resulting suspension preincubated for 30 minutes, cumene hydroperoxide is added in a quantity to have the same above indicated final concentration and at T_{max} is determined the percentage of haemolysis inhibition in the sample from the ratio, multiplied by 100, between the absorbance of the sample containing the erythrocytes, the precursor of B and cumene hydroperoxide respectively and that of the sample containing the erythrocytes and cumene hydroperoxide; the precursors of B meet the test if they inhibit the haemolysis induced by cumene hydroperoxide by a percentage > 15%;

- wherein test 5 which must not be met by the precursor compound of B is an analytical determination carried out by adding aliquots of 10^{-4} M methanol solutions of the precursor of B or B_1 or of $C = -T_C-Y-H$, having the free valence saturated as above indicated, to a solution formed by admixing a 2 mM solution of deoxyribose in water with 100 mM of phosphate buffer and 1 mM of the salt $Fe^{II}(NH_4)_2(SO_4)_2$; after having thermostatted the solution at 37°C for one hour, are added, in the order, aliquots of aqueous solutions of trichloroacetic acid 2.8% and of thiobarbituric acid 0.5 M, heating is effected at 100°C for 15 minutes and the absorbance of the tested solutions is then read at 532 nm; the inhibition induced by the precursor of B or B_1 or $C = -T_C-Y-H$ in the confront of radical production by Fe^{II} is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound and the iron salt and that of the solution containing only the iron salt; test 5 is met when the inhibition percentage as above defined of the B precursor is higher than or equal

to 50%;

provided that in formula (I) when X_2 of B is a linear or branched $C_1 - C_{20}$ alkylene or a cycloalkylene having from 5 to 7 carbon atoms optionally substituted,

the drugs of formula $A = R-T_1$, with the free valence saturated as above described, used in the compound of formula (I), has not to belong to the following classes: drugs for use in incontinence, antithrombotic drugs (ACE inhibitors), prostaglandins, antiinflammatory drugs (NSAIDS and corticosteroids) but not excluding from the antiinflammatory NSAIDS paracetamol and sulindac.

2. Compounds according to claim 1, wherein in the formula $-T_B-X_2-O-$ of the precursor compound of B which meets test 4A and does not meet test 5, X_2 is equal to the $R_{1B}-X-R_{2B}$ radical wherein R_{1B} and R_{2B} , equal to or different from each other, are linear or branched C_1-C_6 alkylenes, or X_2 is a radical wherein two alkylene chains C_1-C_4 , preferably C_1-C_2 , are linked to non adjacent positions of a central ring having 4 or 6 atoms, preferably 5 or 6 atoms, said ring being an unsaturated cycloaliphatic ring, or a saturated or aromatic eterocyclic ring, containing one or two heteroatoms, equal or different, selected from O, S, N. By unsaturated cycloaliphatic ring it is meant a ring that has not an aromatic character according to the Hückel's rule.
3. Compounds according to claims 1 and 2, wherein the precursor compounds of B are:
1,4-butandiol: $HO-(CH_2)_4-OH$,
6-hydroxyhexanoic acid: $HO-(CH_2)_5-COOH$,
4-hydroxybutyric acid: $HO-(CH_2)_3-COOH$,
N-methyldiethanolamine: $HO-(CH_2)_2-N(CH_3)-(CH_2)_2-OH$,
diethylenglycol: $HO-(CH_2)_2-O-(CH_2)_2-OH$,
thiodiethylenglycol: $HO-(CH_2)_2-S-(CH_2)_2-OH$; 1,4 dioxane-2,6-dimethanol, tetrahydropyrane-2,6-dimethanol, 4H pyrane-2,6-dimethanol, tetrahydrothiopyrane-2,6-dimethanol, 1,4-dithiane-2,6-dimethanol, cyclohexene-1,5-dimethanol, thiazole-2,5-dimethanol, thiophene-2,5-dimethanol, oxazole-2,5-dimethanol, preferably N-methyldiethanolamine, diethylenglycol,

thiodiethylenglycol.

4. Compounds according to claims 1-3, wherein the precursor drugs of the compounds of formula (I) are selected from the following: anti-inflammatory, analgesic drugs, bronchodilators and drugs active on the cholinergic system, expectorant-mucolytics, antiasthmatic-antiallergic drugs, antihistaminic drugs, ACE-inhibitors, beta-blockers, antithrombotic drugs, vasodilators, antidiabetic, antitumoral, antiulcer drugs, antihyperlipidemic drugs, antibiotics, antiviral drugs, bone resorption inhibitors, antidementia drugs.
5. Compounds according to claim 4, wherein the precursor drugs are selected from the following:
anti-inflammatory drugs: aceclofenac, acemetacin, acetylsalicylic acid, 5-aminoacetylsalicylic acid, alclofenac, alminoprofen, amfenac, bendazac, bermoprofen, α -bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen, cinmetacin, clidanac, clopirac, sodium diclofenac, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, olsalazine, oxaceprol, oxaprozin, oxyphenbutazone, parsalmide, perisoxal, phenyl acetylsalicylate, pyrazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicilamide O-acetic acid, salicylsulphuric acid, salsalate, sulindac, suprofen, suxibuzone, tenoxicam, tiaprofenic acid, tiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepirac, tomoxiprol;
analgesic drugs: acetaminophen, acetaminosalol, aminochlorthenoxazin, acetylsalicylic 2-amino-4-picoline acid, acetylsalicylsalicylic acid, anileridine, benoxaprofen benzylmorphine, 5-bromosalicylic acetate acid, bucetin, buprenorphine, butorphanol, capsaicine,

cinchophen, ciramadol, clometacin, clonixin, codeine, desomorphine, dezocine, dihydrocodeine, dihydromorphine, dimepheptanol, dipyroceryl, eptazocine, ethoxazene, ethylmorphine, eugenol, floctafenine, fosfosal, glafenine, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, p-lactophenetide, levorphanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nicomorphine, norlevorphanol, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, phenocoll, phenoperidine, phenylbutazone, phenylsalicylate, phenylramidol, salicin, salicylamide, tiorphan, tramadol, diacerein, actarit;

broncodilators and drugs active on the cholinergic system: acefylline, albuterol, bambuterol, bamifylline, bevonium methyl sulphate, bitolterol, carbuterol, clenbuterol, chlorprenaline, dioxethedrine, difylline, ephedrine, epinephrine, eprozinol, etafredine, ethylnorepinephrine, etofylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium bromide, isoetharine, isoprotenerol, mabuterol, metaproterenol, oxybutinyn, oxitropium bromide, pirbuterol, procaterol, protokylol, proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, l-teobromineacetic acid, tiotropium bromide, tretoquinol, tulobuterol, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetrahydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: acetyl-cysteine, ambroxol, bromhexine, carbocysteine, domiodol, erdosteine, ferulic acid, guaiacol, guaifenesin, iodinated glycerol, letosteine, mecysteine hydrochloride, mesna, sobrerol, stepronin, terpin, tiopronin;

antiasthmatic/antiallergic antihistaminic drugs: acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam, chromoglycate, chromolyn, epinastine, fexofenadine, formoterol, histamine, hydroxyzine, levocabastine, lodoxamide, mabuterol, metron s, montelukast, nedocromil, repirinast, seratrodast, suplatast tosylate, terfenadine, tiaramide, urushiol, bromhexine;

ACE-inhibitors: alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril,

enalaprilat, fosinopril, imidapril, lisinopril, losartan, moveltipril, naphthopidil, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, urapidil;

beta-blockers: acebutolol, alprenolol, amosulalol, arotinolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, dilevalol, epanolol, esmolol, indenolol, labetalol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipridalol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol;

antithrombotic and vasoactive drugs: acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betahistine, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, dalteparin, dipyridamole, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, heparin, lamifiban, midodrine, nadroparin, nicotinyl alcohol, nylidrin, ozagrel, perhexiline, phenylpropanolamine, prenylamine, paveroline, reviparin sodium salt, ridogrel, suloctidil, tinofedrine, tinzaparin, triflusal, xanthinol niacinate;

antidiabetic drugs: acarbose, carbutamide, glibornuride glybuthiazol(e), miglitol, repaglinide, troglitazone, 1-butyl-3-metanyl-urea, tolrestat, nicotinamide;

antitumoral drugs: ancitabine, anthramycin, azacitidine, azaserine, 6-azauridine, bicalutamide, carubicin, carzinophilin, chlorambucil, chlorozotocin, cytarabine, daunorubicin, defosfamide, demecolcine, denopterin, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicin, droloxifene, edatrexate, eflornithine, enocitabine, epirubicin, epitiostanol, etanidazole, etoposide, fenretinide, fludarabine, fluorouracil, gemcitabine, hexestrol, idarubicin, lonidamine, mannomustine, melphalan, menogaril, 6-

mercaptapurine, methotrexate, mitobronitol, mitolactol, mitomycins, mitoxantrone, mopidamol, mycophenolic acid, ninopterin, nogalamycin, paclitaxel, pentostatin, pirarubicin, piritrexim, plicamycin, podopillic acid, porfimer sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, thiamiprine, thio-guanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicin;

antiulcer drugs: acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecabet, enprostil, esaprazole, irsogladine, misoprostol, omeprazole, ornoprostil, pantoprazole, plaunotol, rioprostil, rosaprostol, rotraxate, sofalcone, trimoprostil;

anti-hyperlipidemic drugs: atorvastatin, cilastatin, dermostatin, fluvastatin, lovastatin, mevastatin, nystatin, pentostatin, pepstatin, privastatin sodium, simvastatin;

antibiotics: amdinocillin, amoxicillin, ampicillin, apalcillin, apicycline, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoylpas, benzyl penicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin, ceftazopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteteram, ceftezole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephaetrile sodium, cephalixin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cephapirin sodium, cephradine, chloramphenicol, chlortetracycline, cinoxacin, cyprofloxacin, clavulanic acid, clometocillin, cloxacillin, cyclacillin, cycloserine, demeclocycline, dicloxacillin, epicillin, fenbecillin, flomoxef, floxacilli-

n, hetacillin, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, meclocycline, meropenem, metampicillin, methacycline, methicillin sodium, mezlocillin, minocycline, moxalactam, mupirocin, myxin, negamycin, novobiocin, oxacillin, panipenem, penicillin G potassium salt, penicillin N, penicillin O, penicillin V, phenethicillin potassium salt, pipacycline, piperacillin, pirlimycin, porfiromycine, propicillin, quinacillin, ritipenem, rolitetracycline, sancycline, sedecamycine, spectinomycin, sulbactam, sulbenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidin, azithromycin, clarithromycin, dirithromycin, enviomycin, erythromycin, josamycin, midecamycin, miokamycin, oleandomycin, rifabutin, rifamide, rifamycin, rifaximin, rokita-mycin, spiramycin, troleandomycin, viomycin, virginiamycin;

amikacin, apramycin, arbekacin, dibekacin, dihydrostreptomycin, fortimicins, gentamicin, micronomicin, neomycin, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin; bacampicillin, cefcapene pivoxil, cefpodoxime proxetil, panipenem, pivampicillin, pivcefalexin, sultamicillin, talampicillin;

carbomycin, clindamycin, lincomycin, mikamycin, rosaramicin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, flumequine, grepafloxacin, lomefloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rufloxacin, sparfloxacin, tosufloxacin, trovafloxacin, clomocycline, guamecycline, oxytetracycline, nifurpirinol, nifurprazine;

p-aminosalicylic acid, p-aminosalicylic acid hydrazide, clofazimine, deoxydihydrostreptomycin, ethambutol, glyconiazide, isoniazid, opiniazide, phenyl aminosalicylate, rifampin, rifapentine, salinazid, 4-4'-sulfynyldianiline,

acediasulfone, dapsone, succisulfone, p-sulfanilylbenzyl amine, thiazolsulfone, acetyl sulfamethoxypyrazine, mafenide, 4'-(methylsulfamoyl)sulfanilanilide,

salazosulfadimidine, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 2-p-sulfanilylanilinoethanol, N⁴-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfisomidine, sulfisoxazole, 4-sulfanilamido salicylic acid; negamycin, carumonan, cloxyquin, nitroxoline, arginine, metronidazole;

antiviral drugs: acyclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, indanavir, kethoxal, lamivudine, MADU, penciclovir, podophyllotoxin, ribavirin, rimantadine, saquinavir, sorivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine;

bone resorption inhibitors: alendronic acid, butedronic acid, etidronic acid, oxidronic acid, pamidronic acid, risedronic acid;

antidementia drugs: amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

6. Compounds according to claims 4 and 5, wherein the precursor drugs are selected from the following:

anti-inflammatory drugs: acetylsalicylic acid, 5-aminoacetylsalicylic acid, carprofen, diclofenac sodium, diflunisal, etodolac, flufenamic acid, flunixin, flurbiprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, naproxen, niflumic acid, olsalazine, piroxicam, salsalate, sulindac, suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, tolme-

tin, zomepirac, tomoxiprol;

analgesic drugs: acetaminophen, acetylsalicylsalicylic acid, benoxaprofen, buprenorphine, butorphanol, capsaicin, diacerein, dihydrocodeine, ethylmorphine, eugenol, phenylbutazone, meptazinol, morphine, nalbuphine, pentazocine, thiorphan, tramadol, actarit;

bronchodilators and drugs active on the cholinergic system: albuterol, carbuterol, clenbuterol, diphylline, etophylline, fenoterol, ipratropium bromide, metaproterenol, oxybutynin, pirbuterol, salmeterol, terbutaline, tiotropium bromide, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetrahydro-pyridin-4-ylmethyl) acetamide;

expectorant/mucolytic drugs: acetyl-cysteine, ambroxol, bromexine, carbocysteine, guaiacol, ferulic acid, mecysteine hydrochloride, sobrerol;

antiasthmatic/antiallergic antihistaminic drugs: cetirizine, chromoglycate, histamine, levocabastine, lodoxamide, montelukast, terfenadine, bromhexine.

ACE-inhibitors: captopril, enalapril, lisinopril, losartan, ramipril;

beta blockers: alprenolol, atenolol, bupranolol, labetalol, metipranolol, metoprolol, pindolol, propranolol, timolol;

antithrombotic and vasoactive drugs: acetylsalicylic acid, acetorphan, argatroban, clopidogrel, dalteparin, dipyridamole, enoxaparin, heparin, iloprost, midodrine, ozagrel, phenylpropanol amine, trifusal;

antidiabetic drugs: tolrestat, nicotinamide;

antitumoral drugs: anthramycin, daunorubicin, doxorubicin, epirubicin, fluorouracil, methotrexate, vinblastine;

antiulcer drugs: cimetidine, omeprazole, pantoprazole;

antihyperlipidemic drugs: lovastatin, pravastatin sodium, simvastatin;

antibiotic drugs: amoxicillin, ampicillin, aztreonam, biapenem, carbenecillin, cefaclor, cefadroxil, cefamandole, cefatrizine, cefoxitin, clavulanic acid,

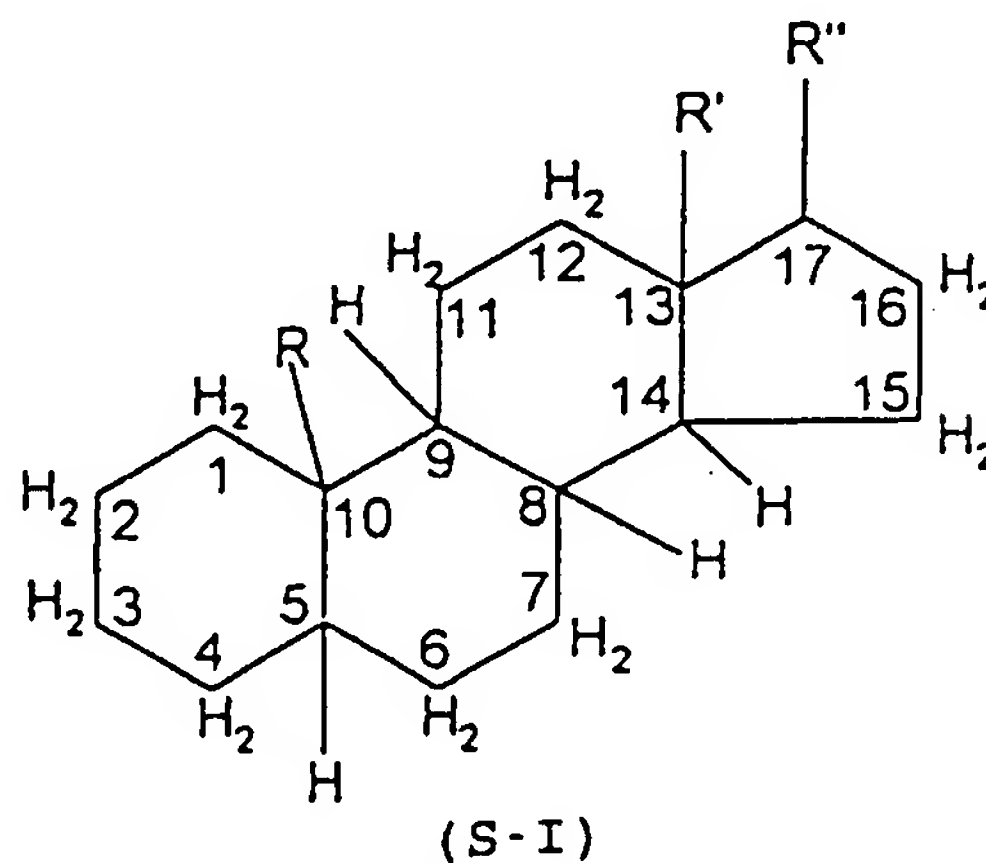
dicloxacillin, imipenem, meclocycline, methacycline, moxalactam, panipenem, sulbactam, azithromycin, erythromycin, josamycin, miokamycin, rifabutine, rifamide, rifamycin, gentamicin, paromomycin, sisomicin, bacampicillin, carbomycin, clindamycin, ciprofloxacin, clinafloxacin, difloxacin, enrofloxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pipemidic acid, apicycline, clomocycline, oxytetracycline, nifurpirinol, nifurprazine, isoniazid, rifampin, rifapentine, dapsone, thiazolsulfone, sulfamethoxazole, sulfamoxole, metronidazole, arginine;

antiviral drugs: acyclovir, famciclovir, ganciclovir, penciclovir, ribavirin, vidarabine, zidovudine;

bone resorption inhibitors: alendronic acid, etidronic acid, pamidronic acid;

antidementia drugs: oxiracetam, tacrine, velnacrine.

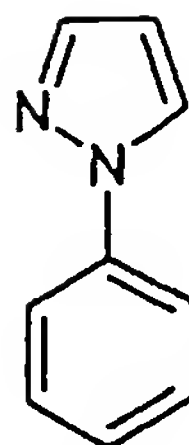
7. Compounds according to claims 1-3 wherein the precursor drugs are steroid compounds wherein A = R- having the following structure:



wherein in substitution of the hydrogens of the CH groups or of the two hydrogens of the CH₂ groups mentioned in the general formula, the following substituents can be present:

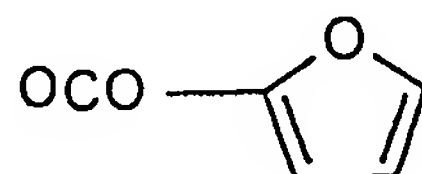
in position 1-2: there may be a double bond;

in position 2-3: there may be the following substituent:



(S-II)

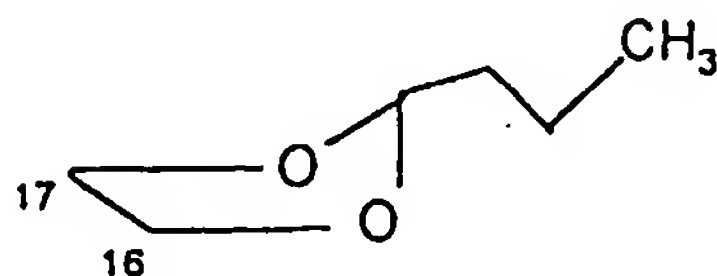
in position 2: there may be Cl, Br;
 in position 3: there may be CO, -O-CH₂-CH₂-Cl, OH;
 in position 3-4: there may be a double bond;
 in position 4-5: there may be a double bond;
 in position 5-6: there may be a double bond;
 in position 5-10: there may be a double bond;
 in position 6: there may be Cl, F, CH₃, -CHO;
 in position 7: there may be Cl, OH;
 in position 9: there may be Cl, F;
 in position 11: there may be OH, CO, Cl, CH₃;
 in position 16: there may be CH₃, OH, =CH₂;
 in position 17: there may be OH, CH₃, OCO(O)_{ua}(CH₂)_{va}CH₃,
 C≡CH or



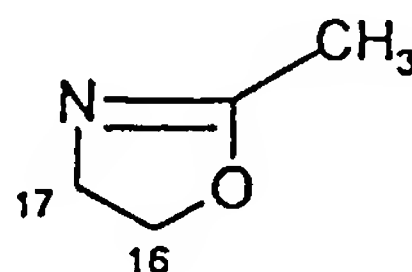
(S-III)

wherein u_a is an integer equal to 0 or 1, v_a is an integer
 from 0 to 4;

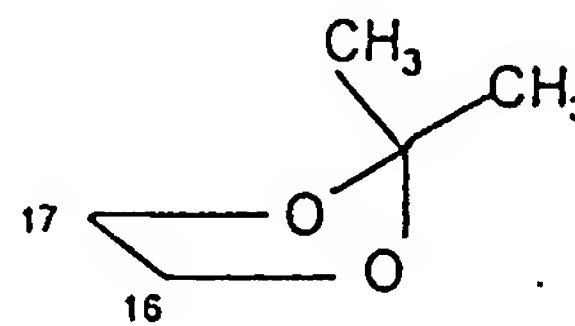
in position 16-17: there may be the following groups:



(S-IVa)



(S-IVb)



(S-IVc)

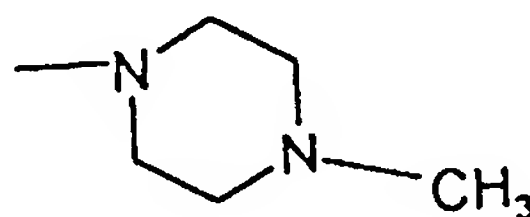
R and R', equal to or different from each other, can be hydrogen or linear or branched alkyls from 1 to 4 carbon atoms, preferably $R = R' = \text{CH}_3$;

R" is $-(\text{CO-L})_t-(\text{L})_{t2}-(\text{X}_0^{\text{I}})_{t1}-$

wherein t, t1 and t2 are integers equal to or different from each other, equal to 0 or 1, with the proviso that when $t = 0$ $t2 = 1$ and when $t = 1$ $t2 = 0$, and that t and t1, or t2 and t1, cannot contemporaneously be equal to 0 when A does not contain -OH groups;

the bivalent bridging group L is selected from:

$(\text{CR}_4\text{R}_5)_{na}(\text{O})_{nb}(\text{CR}_4\text{R}_5)_{n'a}(\text{CO})_{n'b}(\text{O})_{n''b}(\text{CO})_{n'''b}(\text{CR}_4\text{R}_5)_{n''a}$
 wherein na, n'a, and n''a, equal to or different from each other, are integers from 0 to 6, preferably 1-3; nb, n'b, n''b and n'''b, equal to or different from each other, are integers equal to 0 or 1; R₄, R₅, equal to or different from each other, are selected from H, linear or branched alkyl from 1 to 5 carbon atoms, preferably from 1 to 3; X₀^I is X as above defined, or equal to X₂^I wherein X₂^I is equal to OH, CH₃, Cl, N(-CH₂-CH₃)₂, SCH₂F, SH, or



(s-v)

8. Compounds according to claim 7 wherein R" in the formula (S-I) is $-\text{CO}-\text{CH}_2\text{OH}$, or $-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{CH}_2-\text{COOH}$.
9. Compounds according to claims 7 and 8 wherein the precursor steroids are those having the hydroxyl function in position 3 and/or in position 11, and/or having in R" an hydroxyl or carboxylic function in terminal position.
10. Compounds according to claims from 7 to 9 wherein the precursor steroids are selected from the following: Budesonide, Hydrocortisone, Alclomethasone, Algestone, Beclomethasone, Betamethasone, Chloroprednisone, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Cortisone, Corticosterone, Deflazacort, Desonide, Desoximethasone, Dexamethasone, Diflorasone Diflucortolone, Difluprednate, Fluazacort, Flucoronide, Flumethasone, Flunisolide,

Fluocinolone Acetonide, Fluocinonide, Fluocortyn Butyl, Fluocortolone, Fluorometholone, Fluperolone Acetate, Fluprednidene Acetate, Fluprednisolone, Flurandrenolide, Formocortal, Halcinonide, Halobetasol Propionate, Halomethasone, Halopredone Acetate, Hydrocortamate, Loteprednol Etabonate, Medrysone, Meprednisone, Methylprednisolone, Momethasone Furoate, Paramethasone, Prednicarbate, Prednisolone, Prednisolone 25-Diethylaminoacetate, Prednisolone Sodium Phosphate, Prednisone, Prednival, Prednylidene, Rimexolone, Triamcinolone, Triamcinolone Acetonide, 21-Acetoxypregnenolone, Cortivazol, Amcinonide, Fluticasone Propionate, Mazipredone, Tixocortol, Triamcinolone Hexacetonide, Ursodesoxycholic acid, Chenodeoxycholic acid, Mitatrienediol, Moxestrol, Ethynylestradiol, Estradiol, Mestranol.

11. Compounds or salts, or their compositions according to claims from 1 to 10 for use as medicaments; provided that in formula (I) when X_2 of B is a linear or branched $C_1 - C_{20}$ alkylene or a cycloalkylene having from 5 to 7 carbon atoms optionally substituted, the drugs of formula $A = R-T_1$ - with the free valence saturated as above described, used in the compound of formula (I), has not to belong to the following classes: drugs for use in incontinence, antithrombotic drugs (ACE inhibitors), prostaglandins, antiinflammatory drugs (NSAIDS and corticosteroids) but not excluding from the antiinflammatory NSAIDS paracetamol and sulindac.
12. Use of the compounds or salts, or their compositions according to claims 1-10 for the preparation of drugs for the therapeutic stress oxidative application; including, when X_2 of B is a linear or branched $C_1 - C_{20}$ alkylene or a cycloalkylene having from 5 to 7 carbon atoms, the drug of formula $A = R-T_1$ -, with the free valence saturated as described in claim 1, belonging to the following classes: drugs for use in incontinence, antithrombotic drugs (ACE inhibitors), prostaglandins, antiinflammatory drugs.
13. Pharmaceutical formulations containing as active principle the compounds or their salts according to claims 1-10.